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Activation and modulation of automatic response tendencies

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CHAPTER 1
INTRODUCTION

Ein Wort, ein Satz -: aus Chiffren steigen
erkanntes Leben, jäher Sinn,
die Sonne steht, die Spähren schweigen,
und alles ballt sich zu ihm hin.

Ein Wort – ein Glanz, ein Flug, ein Feuer,
Ein Flammenwurf, ein Sternenstrich –
Und wieder Dunkel, ungeheuer,
Im leeren Raum um Welt und Ich.
Gottfried Benn, 1941

In his poem "Ein Wort", Gottfried Benn describes the genesis of a word (or sentence) and the impact it could have on the world. At first, there are only single letters that do not make much sense on their own. If combined with other letters, however, meaning emerges.

In analogy to Benn's poem, the brain's functions and mechanisms would remain largely epiphenomenal if there is no way how these functions can be implemented and realized in the world. The ability to interact with the environment is, therefore, perhaps the

most pivotal function of the human nervous system to give meaning to our thoughts and feelings.

It was early assumed that the brain controls movement. Descriptions of motor impairments after head injuries have been found in writings that date back to the 30th century BCE. Hippocratic doctors recognized that movement difficulties appear on the contralateral side of the injury in the 5th century BCE and Galen of Pergamon was supposedly the first who dissociated between sensory and motor nerves. In the 18th century, Luigi Galvani showed that electrical stimulation of a severed frog's sciatic nerve caused movement of its leg (Taylor & Gross, 2003). This finding generated a number of experiments that sought to investigate the response of other nervous structures to electrical stimulation – most of them were unsuccessful. One of the first proposals that suggested a somatotopically organized (motor) cortex was put forward by John Hughlings Jackson. Jackson studied epileptic seizures and noticed that epileptic convulsions systematically spread from one body part to another, which let him infer that different parts of the cortex affect different muscle groups and that these parts are somatotopically arranged.

One of the first evidence that draws a causal link between the electrical stimulation of the cerebral cortex and movement was put forward by Gustav Fritsch and Eduard Hitzig (Fritsch & Hitzig, 1870). Fritsch and Hitzig applied galvanic stimulation (i.e., a direct current is passed via electrodes to the surface of the brain) above a dog's

exposed cerebral cortex. Strikingly, the temporally brief application of galvanic stimulation produced muscle twitches. Fritsch and Hitzig's experiments revealed that (i) electrical stimulation of some parts of the cerebral cortex caused contralateral movements, thereby confirming previous findings claiming contralateral movement control, (ii) somatotopical organization of the cortex, and (iii) excitable parts of the cortex form a topographical map of body movements (Taylor & Gross, 2003). Fritsch and Hitzig's findings were supplemented by investigations made by David Ferrier. In contrast to Fritsch and Hitzig, however, Ferrier applied faradic stimulation (i.e., alternating current) for longer durations to the brain surface of different kinds of animals. In so doing, Ferrier discovered, for example, that the size of the body representations in the brain is different across species, indicating a close association between behavioral specializations and brain organization. Fritsch and Hitzig's and Ferrier's discoveries were radically against the commonly accepted view "that the striatum was the highest motor center, the cortex was inexcitable, and functional localization in the cortex was phrenological pseudoscience" (Taylor & Gross, 2003, p.339). Nonetheless, the findings that have been made by both Fritsch and Hitzig and Ferrier paved the way for further studies that resulted in important scientific achievements such as the mapping of the (chimpanzee's) motor cortex (Leyton & Sherrington, 1917).

Stimulating the primary motor cortex

The electrical stimulation of the cortex led to the development of a high-voltage electrical stimulator that could activate muscles directly (Merton and Morton, 1980). Using this technique, it became possible to directly stimulate the cortex (and specifically the motor cortex) through the scalp (i.e., transcranial electric stimulation; TES). Although TES was useful for various purposes, the application of it turned out to be relatively painful. Only a couple of years after the development of TES, Barker and colleagues (Barker, Jalinous, & Freeston, 1985) developed a stimulator that could stimulate the brain painlessly through the generation of a magnetic field. Transcranial magnetic stimulation (TMS) was born. Nowadays, TMS has become a major technique to examine brain physiology, but it is applied in clinical settings as well (Hallett, 2007). TMS is a non-invasive brain stimulation technique that can, depending on the specific stimulation protocol, excite or depress particular populations of neurons (for a comprehensive overview of TMS, see Hallett, 2007). Typically, an electrical current accompanied by a short but large magnetic field is running through a coil that is placed over the cortex. The magnetic field, in turn, induces short electrical currents in the human cortex which causes the underlying neuronal populations to discharge (Barker et al., 1985).

When stimulating the motor cortex, the magnetic pulse is followed by descending volleys that travel through the corticospinal (CS) tract. This white matter motor highway terminates at spinal motoneurons that control contralateral peripheral muscles. The CS response that is evoked by the TMS pulse can be quantified using surface electromyography (EMG). The amplitude of the so-called motor evoked potential (MEP) provides a quantification of CS excitability during the time of stimulation. Importantly, however, MEPs are the net result of various contributing processes. Specifically, TMS lacks stimulation precision, which does not only result in the stimulation of CS neurons, but also in the simultaneous stimulation of neighboring cells. These neighboring cells can originate within M1, but they can also stem from more remote brain regions such as premotor or sensorimotor areas, as well as from subcortical areas such as the thalamus or cerebellum (Duque, Greenhouse, Labruna, & Ivry, 2017; Guye et al., 2003). As a consequence, the stimulation of M1 is associated with a complex interplay between CS neurons, intracortical, transcortical and subcortical input at the time of stimulation (Duque et al., 2017). In recent years, effort has been made to disentangle distinct inputs modulating the MEP amplitude. For example, the contribution of intracortical circuits to the size of the MEP has been specified using paired-pulse stimulation protocols (Kujirai et al., 1993) where a subthreshold conditioning pulse is followed by a suprathreshold test pulse after a short delay (between 2 ms and 5 ms). This stimulation

protocol allows to examine GABAergic (i.e., GABA-A; Di Lazzaro et al., 2000) intracortical inhibitory circuits and how this inhibitory circuitry is related to (motor) behavior (Coxon, Stinear, & Byblow, 2006; Duque & Ivry, 2009; Opie, Ridding, & Semmler, 2015). Other measures have examined transcortical circuitry (Ferbert et al., 1992; Rogasch, Daskalakis, & Fitzgerald, 2014) by applying a suprathreshold condition pulse, which results in a transcortical signal modulating the size of the MEP evoked by a second suprathreshold pulse over M1.

Although intracortical, transcortical and subcortical inputs largely contribute to the motor evoked response, signals originating in motor areas are subject to spinal influences as well. After stimulation of the cortex, descending waves (D-wave, I-wave) illustrate the modulatory effect of spinal influences over the MEP amplitude (Di Lazzaro & Rothwell, 2014). Generally, a single D-wave is followed by multiple I-waves at intervals of about 1.5 ms. It was shown that I-waves do not remain after the cortex was removed, whereas D-waves were still observable. This led to the assumption that I-waves are generated within the cortex by postsynaptic excitatory potentials repetitively activating pyramidal neurons (Patton & Amassian, 1953; Terao & Ugawa, 2002), whereas D-waves reflect direct activation of descending CS axons. As a corollary, any combination of D-waves and I-waves could evoke MEPs of a given amplitude (Di Lazzaro & Rothwell, 2014).

To conclude, the magnetic stimulation of M1 involves various processes that all contribute to the amplitude of the MEP. Consequently, one needs to remain aware that MEPs are only an indirect measure of motor cortex (i.e., CS neuron) output. For the remainder of the present dissertation, terms such as "M1 activity" and "CS excitability" will be used interchangeably. That is, these and related terms all refer to the net activation of the motor system that was examined via application of TMS over M1 and quantification of MEP amplitudes.

Cognitive control and automatic response activation

The previous section elaborated on how movement is implemented by our brain to give meaning to our internal processes and thoughts and how we can use TMS to examine the motor system. However, how do various and potentially conflicting internal processes give rise to a single movement? For example, when standing at a crossroad, what mechanism allows us to walk the direct route towards a specific location instead of becoming paralyzed by the sheer amount of available movement alternatives? The ability (or mechanism) to flexibly adjust to environmental demands and to orchestrate available evidence given internal goals is referred to as cognitive control. Cognitive control is an umbrella term comprising various executive processes and mechanisms allowing for goal-directed behavior.

One of the core mechanisms of cognitive control is the control of our impulses. Referring back to the example above, if we need to wait for the traffic light on our side to turn green, cognitive control needs to ensure that we do not start walking as soon as we see any traffic light changing its color (e.g., if the traffic light across the street changes color). Instead, cognitive control must prioritize "our" traffic light, while the influence all other traffic lights have on us must be minimized. The study of prioritization of wanted and task-relevant over unwanted and task-irrelevant factors and how this is achieved has a long-standing history in the field of cognitive control. Tasks investigating this function typically present stimuli that comprise two stimulus features of which only one is task-relevant, while the other feature is irrelevant for task execution (Eriksen & Eriksen, 1974; Simon, 1969; Stroop, 1935). Surprisingly, however, the task-irrelevant stimulus feature automatically affects behavior, such that task performance deteriorates if the task-relevant and task-irrelevant feature are in conflict. For example, in the Simon task (Simon, 1969), a stimulus comprising a task-irrelevant spatial and a task-relevant non-spatial feature is presented (e.g., a blue-colored circle presented in the left hemifield). At the time of stimulus presentation, individuals are required to respond to the task-relevant, non-spatial stimulus feature by pressing a pre-assigned, lateral (i.e., left or right) response key. Typically, it is observed that responses are faster when the (task-irrelevant) spatial stimulus feature corresponds with the location of the response key (i.e., if they are congruent) compared to

when it does not (i.e., if they are incongruent). This observation was ascribed to an automatic activation of response codes that is due to one of two parallel routes that link perception to action (Eimer, 1995; Eimer, Hommel, & Prinz, 1995; Kornblum, Hasbroucq, & Osman, 1990). In this scenario, if stimulus and response features overlap (e.g., stimulus and response location in the Simon task), response codes are automatically activated via a direct route, while appropriate and deliberate response selection is implemented via an indirect route that links stimulus-response codes in an arbitrary fashion. Consequently, if the stimulus location is incongruent with the actual response location, conflict arises in the information processing system as a result of competition between response alternatives that both compete for execution. To ensure goal-directed behavior, heightened cognitive (or attentional) control is deployed to overcome such conflict in the information processing stream (Cohen, Dunbar, & McClelland, 1990; Mackie, Van Dam, & Fan, 2013; Shiffrin & Schneider, 1977). One influential theory that explains how conflict arises and is resolved is the conflict-monitoring theory (CMT; Botvinick, Braver, Barch, Carter, & Cohen, 2001). This theory proposes a system that detects and resolves conflict by an upregulation of cognitive control. Conflict detection (or monitoring) is assumed to be located in the anterior cingulate cortex (ACC), while the upregulation of control is implemented by the dorsolateral prefrontal cortex (DLPFC).

Evidence of automatic response activation and conflict have also been observed in the motor system when examining CS excitability. For instance, it has been shown that on conflict trials the task-irrelevant stimulus location evoked an early transient rise in CS excitability suggesting a fast but transient preparation of the inappropriate response within the motor system (van Campen, Keuken, van den Wildenberg, & Ridderinkhof, 2014). Likewise, others have reported a similar pattern of early activation of inappropriate response representations during incongruent trials biasing CS excitability for the Eriksen flanker conflict paradigm (Michelet, Duncan, & Cisek, 2010; Verleger, Kuniecki, Möller, Fritzmannova, & Siebner, 2009). These findings thus suggest that the motor system may be subject to stimulus-driven processes affecting CS excitability in a fast and direct way, which may result in the activation of prepotent but unwanted response tendencies. In extension to these findings, the present dissertation will examine whether and how irrelevant information influences the motor system when no motor output is required.

Cognitive control and action selection and preparation

The previous paragraph discussed the importance of cognitive control to keep automatic influences interfering with our goals in check to avoid impulsive and unwilled behavior. However, cognitive control is also necessary for the selection and preparation of viable goal-directed actions (Braver, 2012; Ridderinkhof, van den

Wildenberg, Segalowitz, & Carter, 2004; Schumacher, Elston, & D'Esposito, 2003), thereby inhibiting other less viable action alternatives (Aron, 2007; Aron et al., 2007; Aron, Robbins, & Poldrack, 2014). Referring back to the example above, the goal-directed selection of an appropriate action and the inhibition of inappropriate actions from the pool of action alternatives may result in the prioritization of a walking-movement over all other possible movements (e.g., jumping) when crossing the street. However, such action selection does not only include the specification of an appropriate movement as such, but also involves the orchestration of various decision-related factors influencing the selection of a specific movement as well. For example, if we are pressed for time because the bus that we want to take is already waiting at the other side of the street, efficient selection of movement in accordance with our goals is indispensable. In this context, cognitive control may help to prioritize a "running-movement" over a "walking-movement", because otherwise chances are that our goal to reach the bus in time is not met.

Traditionally, action selection is assumed to be the result of serial information processing stages that temporally separate perception, decision and action from each other (Flash & Hogan, 1985). More recent accounts, however, argue that decision processes continuously bias action selection (Cisek, 2006, 2007, 2012; Cisek & Kalaska, 2010), and it has indeed been shown that decisions modulate action selection before movement onset (e.g., Donner, Siegel, Fries, &

Engel, 2009). In the light of current goals, cognitive control needs to ensure that the competition between action alternatives fueled by decision-related factors results in the selection of optimal choices. Of course, when under time pressure, such action selection can go awry, resulting in performance errors (e.g., Danielmeier & Ullsperger, 2011) or potentially serious consequences.

One way to ensure correct action selection is by preparing the appropriate action in advance. The preparation of future events and actions allows us to flexibly meet environmental demands (Bode & Haynes, 2009; Brass & Von Cramon, 2002) and comes with an evolutionary advantage as it allows individuals to implement actions fast and accurately (Sudevan & Taylor, 1987). The advance preparation of actions could be labeled as a form of proactive cognitive control. In his dual-mode framework, Braver (2012) argued that proactive control selects and maintains goal-relevant information in order to optimally bias perceptual and action systems before action. Reactive control, in contrast, is supposed to be engaged only if there is an actual need for deployment of control. While proactive control can be conceptualized as a sort of 'early selection' that anticipates future demands, reactive control forms a mechanism of 'late correction' that deploys attentional resources only after the occurrence of a demanding event.

A wealth of research has been conducted to examine the motor system during action selection and preparation. One of the typical setups to examine selection and preparation is a cue-target delay

paradigm in which an (un)informative cue signals which response must be made (and which effector must be used) after a short delay period at the onset of an imperative signal (Duque & Ivry, 2009). To examine the state of the motor system during the preparation of a specified (or unspecified) action, TMS is typically applied at some point(s) throughout the delay period over M1, and concurrent EMG is recorded from one (or multiple) relevant muscles using surface electrodes. Typically, during such motor preparation a reduction of CS excitability is observed close to the onset of the imperative signal (Duque & Ivry, 2009; Duque, Labruna, Cazares, & Ivry, 2014; Duque, Labruna, Verset, Olivier, & Ivry, 2012; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010; Hasbroucq, Kaneko, Akamatsu, & Possamai, 1999; Labruna et al., 2014; Sinclair & Hammond, 2009). The reduction of CS excitability throughout the delay period varies as a function of delay period duration (Lebon et al., 2015) and may be sensitive to response complexity (Greenhouse, Saks, Hoang, & Ivry, 2015). Thus, action selection and preparation have direct consequences on motor system (at least in terms of CS excitability). However, what is the influence of goal-relevant variables that bias action selection and preparation? For instance, what would change in our motor system during selection and preparation if we had no or even more time pressure, if we were in pain, if we were sad or exceptionally happy, or if our action would promise reward? The present dissertation largely focusses on the question how motivation, and specifically reward, affects CS excitability during action selection and preparation.

Reward and the motor system

Reward is a strong motivator that guides behavior. If associated with reward, responses typically become faster and more accurate. In numerous studies, researchers have sought to examine how reward processing is reflected in the brain. At the core of the brain's reward system lie structures such as the anterior cingulate cortex, orbital frontal cortex, ventral striatum, ventral pallidum, and midbrain dopaminergic neurons comprising the cortical-basal ganglia circuit (Haber & Knutson, 2010). Amongst others, amygdala, hippocampus, and thalamus are supposed to regulate the reward circuit. The neurotransmitter dopamine (DA) inherits a particularly prominent role during reward processing. Dopaminergic neurons have been found to discharge in response to reward, but also during the anticipation of reward in both monkeys (Mirenowicz & Schultz, 1994; Schultz, 1998) and humans (Schott et al., 2008). However, only little is known about the (potential) effects of reward anticipation on M1 and how this may be modulated by DA (Luft & Schwarz, 2009). The few studies that have examined CS excitability in response to reward have shown an increase of CS excitability during reward anticipation (Chiu, Cools, & Aron, 2014; Gupta & Aron, 2011) and CS excitability increases as a function of reward probability, although this pattern may be contingent on the task at hand (Mooshagian, Keisler, Zimmermann, Schweickert, & Wassermann, 2015). In contrast, other

studies did not find that a reward-contingent modulation of CS excitability but reported a change in other measures such as SICI (Kapogiannis, Campion, Grafman, & Wassermann, 2008; Thabit et al., 2011). Thus, the few studies that have made an effort to examine CS excitability in response to reward form a largely heterogeneous collection of studies comprising diverse stimulation protocols and timings as well as variable reward characteristics (e.g., primary versus secondary rewards). The present dissertation aimed to systematically examine the effect of reward anticipation on CS excitability.

Research goals and outline of the present dissertation

The goal of the present dissertation was, first, to investigate if and how the motor system reflects (automatic) information processing in the absence of any overt motor output (chapter two). Second, it was examined if and how CS excitability may be modulated by higher-level cognition and decision-related factors such as motivational states (induced by variable amounts of response-contingent reward) prior to any motor output (chapter three until chapter six).

More specifically, in **chapter two**, we investigated whether CS excitability was affected by the mere perception of a task-irrelevant spatial word that was not associated with any motor output. In other words, we tested the extent to which abstract spatial concepts bias CS excitability even though these concepts did not require an actual motor-response. This experimental approach can be viewed as an

extension to the above-mentioned findings of early and transient activation of the inappropriate response representation within M1 during the presentation of incongruent Simon (van Campen et al., 2014) or Flanker (Michelet et al., 2010; Verleger et al., 2009) stimuli. To that end, a colored circle was presented at the center of the computer screen on half of all trials, whereas on the other half of all trials, spatial words (i.e., LEFT, RIGHT) or a non-word (i.e., XXXXX) was presented. Participants were asked to respond with a bimanual button press when they perceived a colored circle, and not to respond at all when (non-)words were presented. Importantly, on (non-)word trials, TMS was applied over left or right M1 and EMG was obtained from the contralateral first dorsal interosseous (FDI) muscle. Results showed a CS excitability congruency effect (i.e., relatively increased CS excitability when the stimulated M1 controls the FDI that was congruent with the semantics of the spatial word, and relatively decreased CS excitability when the FDI controlled by the stimulated M1 was incongruent with the spatial concept). These findings suggested that CS excitability can be modulated by the mere perception of task-irrelevant and abstract stimuli that do not demand any actual motor output.

Given the observed CS excitability compatibility effect, chapter two called for further investigation. In **chapter three**, we examined whether CS excitability congruency effects could be modulated by decision-related variables, and, specifically, whether different states of motivation could modulate such congruency effects. To that end,

we employed a cue-target delay paradigm using Simon stimuli as targets, which usually induce a strong behavioral congruency effect. At the beginning of each trial, a (non-)reward cue was presented, indicating whether or not participants could accumulate extra reward for fast and accurate target performance. The motivational cue was followed by a short delay period and the target presentation. CS excitability was assessed at three different timings throughout the delay period, as well as shortly after target onset. Neither behaviorally nor in terms of CS excitability was the size of the congruency effect modulated by motivation. Strikingly, however, CS excitability was strongly modulated by reward-anticipation throughout the delay period. More specifically, it was observed that reward compared to non-reward anticipation was associated with increased CS excitability soon after the motivational cue was presented, and followed by a CS excitability decrease resulting in relatively less CS excitability shortly before target onset. These results suggested that the preparation of a task or an action could be modulated by decision-related factors such as the anticipation of a reward.

The experiment described in **chapter four** was designed to replicate the results of the experiment described in chapter three. Furthermore, chapter four tried to clarify whether the finding that the congruency effect was not modulated by reward (chapter three) was specific to the chosen (Simon) task. Accordingly, we replicated the task design from chapter three, but substituted the Simon target

stimuli with Stroop target stimuli. Behaviorally, results showed that reward modulated the size of the congruency effect, which was especially true to slow reaction times. However, CS excitability throughout the cue-target delay period was not differentially modulated by reward. Although surprising, results seemed to portend that task-characteristics (e.g., task difficulty) may obscure the extent to which the prospect of receiving additional reward influences preparatory CS excitability.

The results described in chapter three were somewhat surprising as they revealed an unanticipated CS excitability increase early after the onset of the reward-promising cue. Therefore, in **chapter five** we investigated whether this early CS excitability increase was intrinsic to the anticipation of reward or due to the preparation of an actual response. This was examined in two experiments that modulated time pressure in Go-trials through different time-out procedures. In both experiments, preparatory CS excitability was attenuated for Go compared to NoGo trials, indicating that preparatory CS excitability is strongly modulated by the preparation of an actual action. Interestingly, only the imposition of a strict time-out procedure in Exp. 2 resulted in CS excitability being largest during reward anticipation for Go responses for the early stimulation epoch and then sharply decreased, while CS excitability remained unchanged during non-reward anticipation.

The previous chapters indicated that reward alters preparatory CS excitability under specific circumstances. However, preparatory

CS excitability changes could be due to changes in CS excitability, changes in inhibitory circuits, or both. To that end, **chapter six** investigated whether reward alters preparatory short intracortical inhibition (SICI) during the delay period of a cue-target-delay paradigm. Results did not show such modulation of SICI by reward, which tentatively suggests that preparatory CS excitability changes are not associated with changes in inhibitory circuits.

Finally, the general discussion (**chapter seven**) will summarize the findings across the individual chapters. Moreover, implications of the described work as well as potentially future experiments will be discussed.

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CHAPTER 2

IT WASN'T ME! MOTOR ACTIVATION FROM IRRELEVANT SPATIAL INFORMATION IN THE ABSENCE OF A RESPONSE[1]

Embodied cognition postulates that perceptual and motor processes serve higher-order cognitive faculties like language. A major challenge for embodied cognition concerns the grounding of abstract concepts. Here we zoom in on abstract *spatial* concepts and ask the question to what extent the sensorimotor system is involved in processing these. Most of the empirical support in favor of an embodied perspective on (abstract) spatial information has derived from so-called compatibility effects in which a task-irrelevant feature either facilitates (for compatible trials) or hinders (in incompatible trials) responding to the task-relevant feature. This type of effect has been interpreted in terms of (task-irrelevant) feature-induced response activation. The problem with such approach is that incompatible features generate an array of task-relevant and –irrelevant activations [e.g., in primary motor cortex (M1)], and lateral

[1] Bundt, C., Bardi, L., Abrahamse, E. L., Brass, M., & Notebaert, W. (2015). It wasn't me! Motor activation from irrelevant spatial information in the absence of a response. *Frontiers in Human Neuroscience, 9*.

hemispheric interactions render it difficult to assign credit to the task-irrelevant feature *per se* in driving these activations. Here, we aim to obtain a cleaner indication of response activation on the basis of abstract spatial information. We employed transcranial magnetic stimulation (TMS) to probe response activation of effectors in response to semantic, task-irrelevant stimuli (i.e., the words left and right) that did not require an overt response. Results revealed larger motor evoked potentials (MEPs) for the right (left) index finger when the word *right* (*left*) was presented. Our findings provide support for the grounding of abstract spatial concepts in the sensorimotor system.

INTRODUCTION

Embodied cognition interprets cognition as grounded in sensorimotor representations. This perspective on cognition has been supported, for example, by studies that demonstrated effector-specific activation of sensorimotor cortices during reading of action related words (Hauk, Johnsrude, & Pulvermüller, 2004; Hauk & Pulvermüller, 2004). Specifically, when the meaning of a verb is strongly linked to a specific action (e.g. "kick, "pick"), mere reading of the verb evokes activation in cortical areas that are active during the actual execution of the respective action (Hauk & Pulvermüller, 2004). Furthermore, sensorimotor grounding has been found in action sentence comprehension (Aziz-Zadeh, Wilson, Rizzolatti, & Iacoboni, 2006), and during auditory perception of action sentences (Buccino et al., 2005; Tettamanti et al., 2005).

While there exists ample support for sensorimotor grounding of concrete stimuli, there is an ongoing debate about how and to what extent abstract concepts are grounded in sensorimotor systems (for a review see Kiefer & Pulvermüller, 2012; Pecher, Boot, & Van Dantzig, 2011). For instance, the processing advantage (e.g. recall performance in memory tasks) for concrete over abstract concepts has been explained by proposing that concrete concepts are based on visual imaginary and verbal symbolic codes, while abstract concepts are only linked to the latter codes (Paivio, 1991). In order to relate abstract concepts to sensorimotor representations, frameworks were

developed based on semantic processors that handle interpretation of concrete as well as abstract concepts (Mahon & Caramazza, 2008). Other frameworks emphasized the relevance of linguistic context (Schwanenflugel & Shoben, 1983), or focused on simulation of concrete situations that instantiate abstract concepts (Barsalou & Wiemer-Hastings, 2005). Thus, there exist diverse opinions about how abstract concepts are grounded in sensorimotor systems. Despite the ongoing controversy, understanding how (if at all) abstract concepts are represented in sensorimotor systems exemplify an important test case for the question whether concepts are embodied as a rule (e.g. Dove, 2015), and as such determines the reach of embodied cognition in general. Here we zoom in on the question about whether abstract spatial concepts ('left' and 'right') are laid down in the sensorimotor system. Specifically, we investigate whether the processing of the words left and right is directly reflected in primary motor cortex (M1) activation. Previous research has delivered a number of indications that such M1 activation can be expected, though this conclusion has not yet been confirmed conclusively. Now we will first outline the previous work that we build on.

Empirical evidence has shown that motor responses were modulated by implicit spatial stimulus features such as location, which may provide a first indication of an association between spatial stimulus information and spatially defined motor activation. The link between spatial stimulus information and motor responses has a long

history in spatial compatibility research where responses to the task-relevant features are influenced by the processing of task-irrelevant spatial location of the stimulus (Hommel, 2011; Lu & Proctor, 1995). When the stimulus location feature is incompatible with the correct response side, reaction times (RTs) are longer and errors increase. Conversely, on compatible trials RT and error performance typically improves. Thus, incompatible stimulus-features can have a significant impact on goal-directed behavior. Interestingly, the performance decrease on incompatible Simon trials was shown to be accompanied by an (initial) ipsilateral activation of motor cortices (Valle-Inclán & Redondo, 1998; Vallesi, Mapelli, Schiff, Amodio, & Umilta, 2005). This could indicate that the task-irrelevant location feature initially triggers its corresponding motor activation. Similarly, a transcranial magnetic stimulation (TMS) – electromyography (EMG) study supports these findings by showing that stimulus location on incompatible trials in the Simon task is linked to heightened corticospinal excitability for the non-involved hand (van Campen, Keuken, van den Wildenberg, & Ridderinkhof, 2014). Thus, these studies suggest that there exists an association between (task-irrelevant) spatial stimulus information and spatially defined motor activation.

Furthermore, there is some indication that the semantic interpretation of spatially defined categories such as above or below interacts with the processing of location information. In a variant of the spatial Stroop task individuals are asked to respond to the

location of a word that is compatible or incompatible with its meaning; for example, the word above printed above (compatible) or below (incompatible) a reference point (Luo & Proctor, 2013; O'Leary & Barber, 1993; Seymour, 1973). Responses to incompatible stimuli are typically slower than responses to compatible stimuli because the task-irrelevant word is processed which facilitates or interferes with responding to the relevant feature. This interaction indicates a link between semantics and stimulus location processing. More specifically, it suggests that both accessing stimulus semantics and the processing of stimulus location modulates motor activation and compete with each other (presumably) at the motor output level. One study using the spatial Stroop task in combination with the event-related optical signal (EROS) technique reported that stimulus semantics could generate activation at the level of the M1 (DeSoto, Fabiani, Geary, & Gratton, 2001), which suggests that spatial categories may be grounded in the sensorimotor system. In this study, a cue at the beginning of each trial determined which stimulus feature (i.e. semantics or location) was relevant on the current trial and individuals were asked to provide a response according to the relevant feature. However, DeSoto and colleagues did not distinguish between these two trial types; instead, they based their analysis on motor cortex activation during compatible and incompatible trials across the two tasks. Activation of M1 may have been based on both stimulus-driven response competition and response execution, which makes it impractical to investigate the isolated impact of single

stimulus features (e.g. semantics) on M1 activation. Specifically, M1 activation may be confounded by competitive response execution processes that are due to the processing of two (potentially competing) stimulus features that both generate M1 activation.

In line with the findings from the spatial Stroop paradigm, other studies demonstrated that the processing of semantic, spatially defined categories could influence motoric components such as reaching and grasping kinematics (Gentilucci, Benuzzi, Bertolani, Daprati, & Gangitano, 2000; Gentilucci & Gangitano, 1998; Glover & Dixon, 2002; Glover, Miall, & Rushworth, 2005; Glover, Rosenbaum, Graham, & Dixon, 2004; Till, Masson, Bub, & Driessen, 2014). For instance, Glover and Dixon (2002) showed that the processing of the words large or small could modulate grip aperture early in the reaching movement. This effect was also found when words implicitly referred to large or small graspable objects (Glover et al., 2004). These studies suggest that semantic classifications could activate motor tendencies and translate to reaching and grasping kinematics. The neural analogue of semantic classification was not investigated in these studies, and similarly to the studies mentioned above, results were contingent on interference effects (i.e. properties of the graspable object interfered with semantic classification) and response execution. Thus, the specific role of M1 during semantic classification remains unclear.

The reviewed studies show that i) implicit stimulus location – although task-irrelevant – changes motor activation, ii) accessing

semantic spatial information such as above may interact with motor activation that was generated by stimulus location, and iii) processing abstract semantic stimuli such as large modulates motoric components like reaching and grasping kinematics. These studies all suggest a link between spatial information and motor activation and provide support for sensorimotor grounding of spatial information (location as well as more abstract semantic concepts). However, all of these studies made use of a compatibility paradigm where irrelevant information interacts with an overt response. Therefore, the observed effects are difficult to interpret as they might reflect complicated interactions between the processing of relevant and irrelevant information. Furthermore, in the studies that measured activation in motor areas of the brain, brain activation patterns may be confounded by stimulus-driven response competition resulting in overt response execution. More specifically, incompatible features generate an array of task-relevant and –irrelevant activations (e.g., in M1), and lateral hemispheric interactions (Chen, 2004) render it difficult to assign credit to the task-irrelevant feature per se in driving these activations. This is the reason why in these studies the isolated effect of single spatial stimulus features or single abstract spatial concepts on motor activation is impractical to examine. It remains unclear, therefore, to what extent the processing of abstract spatial concepts – like the words left or right – can generate spatially defined motor activation when response execution and stimulus-driven response competition is prevented.

As noted above, the present study sought to investigate whether the processing of (abstract) semantic concepts is reflected in M1 activation, even when no overt response is required. In our set-up, participants are passively watching the words left or right presented centrally on the screen, while we measure whether this induces corresponding motor activation. Importantly, from behavioral studies we know that participants need to be engaged in a left-right discrimination task before we can observe activation on the basis of horizontal spatial information (Ansorge & Wühr, 2004, 2009; Hommel, 1996; Wühr & Ansorge, 2007; Zhao, Chen, & West, 2010). Therefore, we implemented trials where participants had to respond with a left or right keypress to colored circles. These trials were implemented so that a left-right discrimination was part of the overall task set, even though we measured motor activation on trials were no response was required. On word trials, spatial words LINKS (Dutch for left) or RECHTS (Dutch for right) or non-words (XXXXX) were presented and participants were instructed to ignore these irrelevant stimuli. During these trials, TMS was applied to assess corticospinal excitability and motor evoked potentials were recorded from the left and right first dorsal interosseus (FDI). It was predicted that the respective FDI would be more activated by a compatible (e.g. right FDI and RECHTS) compared to an incompatible word (e.g. right FDI and LINKS), extending previous findings of the effect of task-irrelevant information on cognition.

Methods

Participants

22 healthy, Dutch native speakers took part in the current study (20 female; mean age: 21.19 ± SD: 1.83) and were paid for their participation (35€). All participants gave written informed consent according to the declaration of Helsinki, had normal or corrected-to-normal vision and were prescreened for psychological, neurological and other factors that could interfere with a safe application of TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Four participants were excluded from the final sample; two participants due to technical failure and two more because of an insufficient number of word (i.e. TMS) trials (see data analysis section below). The study was approved by the Medical Ethical Review Board of the Ghent University Hospital.

TMS stimulation and EMG recordings

EMG was obtained from the left and right FDI muscle, which is relevant for abducting the index finger away from the middle finger. EMG activity was recorded using the ActiveTwo system (www.biosemi.com). Sintered 11 × 17 mm active Ag-AgCl electrodes were placed over the right and left FDI, and reference electrodes were placed over the metacarpophalangeal joints, respectively. Furthermore, the ground-electrode was mounted onto the back of the right hand close to the wrist joint. The EMG signal was amplified

(internal gain scaling) and digitized at 2048 Hz. Furthermore, a high-pass filter of 3 Hz was applied. For further offline analyses, resultant data was stored on a separate personal computer. A biphasic stimulator (Rapid2; The Magstim Company Ltd.) and a 70 mm figure of eight coil were used to deliver TMS pulses (for implications of TMS stimulation see Bestmann & Duque, 2015; Bestmann & Krakauer, 2015). The coil was held tangentially over the left (or right) hand motor area. The coil handle pointed backward and built an angle of 45° with the sagittal plane and was held by a mechanical arm during the experiment. The scalp location of TMS stimulation was dependent on the position at which the most reliable MEP was obtained. For each hemisphere, the intensity that evoked MEPs larger than 50 μV in 50% of the cases was defined as the resting motor threshold (rMT) (Rossini et al., 1994) and determined the eventual TMS stimulation intensity for each subject and hemisphere. During the experiment, the stimulation intensity was set at 120% of the rMT (left M1 rMT: 54.94%; right M1 rMT: 54.16%). On average, the intensity was 64.18% (range 49% - 80%) of the maximal stimulator output. Subjects were outfitted with a swimming cap on which the location of TMS stimulation was highlighted. Using this method, the experimenter was able to continuously monitor the location of TMS stimulation.

Stimuli and procedure

Participants were seated in a comfortable armchair in a darkened and noise-shielded room. Participants were asked to put the tips of each index finger between two buttons (between F4 key and F5 key, and between F8 key and F9 key respectively) on a reversed standard QWERTY keyboard (for a similar procedure see Klein, Olivier, & Duque, 2012; Klein, Petitjean, Olivier, & Duque, 2014). Furthermore, participants were instructed to provide a bimanual choice after the presentation of a relevant stimulus (specified further below), by performing an abduction movement with either the left or right index finger away from the middle-finger and towards a medial response button (F5 key and F8 key) to eventually execute a key press.

Experimental stimulus presentation was carried out on a 17-inch computer monitor (1024 x 768 pixels) using Presentation® software (Version 16.3, www.neurobs.com) Half of all trials (N = 384) were color (i.e. non-TMS) trials, whereas the other half were word (i.e. TMS) trials.

During color trials (i.e. non-TMS trials; Figure 1A) a presentation cross was presented for 500 msec. after which a red or a green circle (height and width: 1.7°) was presented centrally on the screen for maximally 1000 msec, upon which the participant had to provide a response according to the color of the stimulus. If the participant did not respond within the 1000 msec stimulus

presentation window, a "too late" screen was presented for 1000 msec. On word trials (Figure 1B) the presentation of a fixation cross for 500 msec was followed either by a word inheriting spatial semantics (i.e. RECHTS; LINKS; Dutch for right and left respectively) or by a nonspatial control-word (i.e. XXXXX) (height: 0.7°; width: maximally 3.8°) displayed for 1000 msec. A TMS pulse was delivered after one of four stimulus-pulse intervals (250, 320, 500, or 640 msec; c.f.Catmur, Walsh, & Heyes, 2007). This resulted in 16 TMS pulses that were applied per hemisphere, condition, and timing (see data analysis section). Crucially, participants were instructed not to provide any response during word trials. Individual trials were separated by a jittered inter-trial-interval (ITI) of 1000 – 1500 msec.

In total, participants needed to complete six blocks of 128 pseudo-randomized trials, respectively. Each block was separated by a one-minute break. After three blocks, the stimulated hemisphere was changed. The order of hemisphere stimulation was counterbalanced across participants. In total, the experiment took about 1.5 hours.

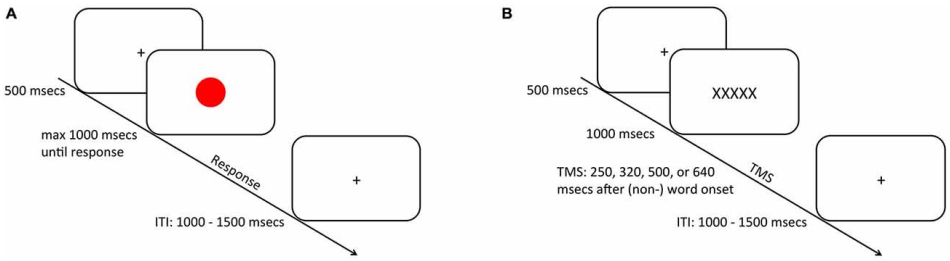

Fig 1. Schematic representation of the trial procedure. During half of the trials (A), subjects were required to respond via a bimanual key press to the ink-color of a centrally presented circle that was presented for maximally 1000 msecs depending on the speed of participant's response. On the other half of the trials (B), a (non-) spatial word was presented upon which the subjects did not provide any overt response. After one of four intervals (250, 320, 500, 640 msecs) a TMS pulse was applied over the primary motor cortex to probe motor cortex excitability. Trials were separated by an inter-trial-interval that was jittered between 1000 and 1500 msecs.

Data analysis

Peak-to-peak amplitude of the MEP was calculated for each trial. EMG epochs starting 500 msec before and ending 500 msec after the actual event (i.e. the TMS pulse) were extracted from the recorded data. Trials were checked for background EMG activity during a time window of 500 msec preceding the TMS pulse. The trial was rejected if background EMG activity was found during this window. Using MATLAB software, peak-to-peak MEP amplitude of each trial was calculated for the 20-40 msec window following a TMS pulse (i.e. this

is the typical time range at which a MEP occurs). Subsequently, the total number of trials that survived preprocessing was calculated for each subject. The (population) mean number of trials was 13.79 (*SD* ± 3.24) averaged across all conditions and subjects. Subjects were removed from further analysis when the mean amount of trials across all conditions fell two standard deviations or more below the average number of trials across all subjects and conditions (N = 2 individuals). Thus, the final sample on which statistical analyses were performed consisted of 18 individuals. On average, this procedure resulted in 14.37 (*SD* ± 2.46) trials per condition (i.e. stimulated hemisphere, compatibility and TMS timing). Moreover, due to the highly variable nature of MEPs in participants and to avoid MEP amplitude variability affecting subsequent analyses unevenly Z-scores normalization was performed (Burle, Bonnet, Vidal, Possamai, & Hasbroucq, 2002; van den Wildenberg et al., 2010) (Burle et al., 2002; van den Wildenberg et al., 2010). First, the mean and the standard deviation were calculated for all valid trials (i.e. trial population mean) per participant. Thereafter, Z-scores were computed by subtracting the trial population mean from the individual trial MEP amplitude and dividing it by the trial population standard deviation of the respective subject. Z-scores were then averaged per condition and subject. Resulting MEP data were submitted to a 2×3×4 repeated measures ANOVA with hemisphere (left, right) × compatibility (compatible, incompatible, neutral) × timing (250, 320, 500, 640 msec) as within-subject factors. Potential effects were further investigated

using paired-sample *t*-tests. All statistical tests were carried out using SPSS (Version 22.0. Armonk, NY: IBM Corp). The statistical significance threshold was set to $p = 0.05$. Whenever necessary, the Greenhouse-Geisser epsilon correction as well as the Bonferroni correction were applied.

RESULTS

Color trials. The mean reaction time and the mean proportion of correct responses were 591.04 msecs (*SD* ± 39.92) and 98.13% (*SD* ± .016) respectively.

Word trials. Figure 2 shows the normalized Z-score MEP amplitudes averaged over hemisphere and stimulation interval for each specific stimulus during word trials (see Figure 3 for raw MEPs). Results indicate a main effect of compatibility ($F(2,34) = 3.613$, $p = 0.038$, $\eta p^2 = 0.175$). A paired-sample *t*-test indicates a significant difference between compatible and incompatible stimuli ($t(17) = 3.101$, $p = 0.006$, $r^2 = 0.361$). This illustrates increased MEPs for the left (right) index finger when the word LEFT (RIGHT) is presented compared to when the word RIGHT (LEFT) is presented. The difference between compatible trials and neutral, and incompatible trials and neutral trials did not reach significance, ($t(17) = 0.825$, p = 0.421) and ($t(17) = -1.606$, $p = 0.127$), respectively.

Furthermore, a main effect of stimulation interval was observed ($F(1.758,29.889) = 5.157$, $p = 0.015$, $\eta p^2 = 0.233$), indicating a reverse relationship between MEP amplitude and stimulation interval. No effect of hemisphere, however, was observed ($F(1,17) = 0.488$, $p = 0.494$, $\eta p^2 = 0.048$), and none of the interactions reached significance ($p > 0.05$).

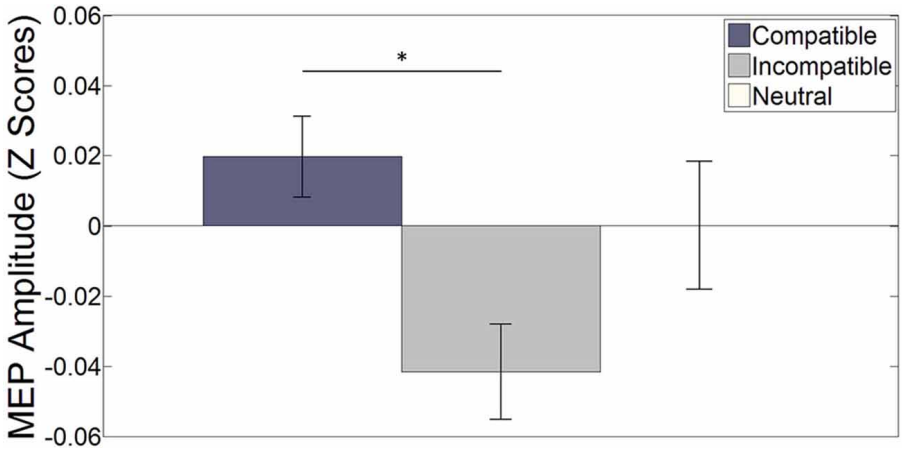

Fig 2. The bar plot shows the effect of (non-) spatial words on the (in-) compatible effector averaged over both hemispheres and all four stimulation intervals. Error bars depict the standard error of the mean. On average, MEP amplitudes were larger for compatible stimuli compared to incompatible stimuli ($t(17) = 3.101$, $p = 0.006$). The difference between compatible and neutral and incompatible and neutral stimuli did not reach significance ($t(17) = 0.825$, $p = 0.421$) and ($t(17) = -1.606$, $p = 0.127$) respectively.

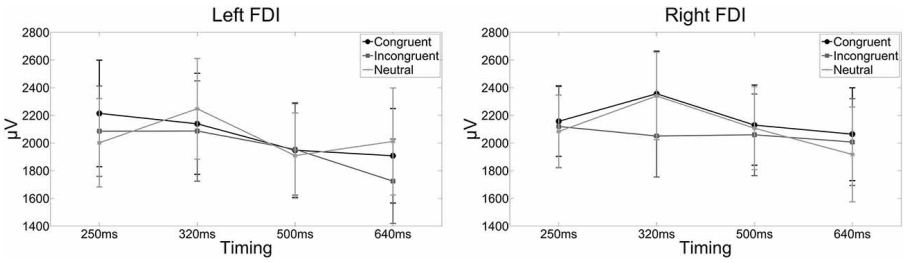

Fig 3. The line graphs show the raw MEP amplitudes for each condition and FDI for illustrative purposes. Error bars indicate standard errors of the mean. Actual statistical tests were run on the Z scores only. The left line graph shows the raw MEP amplitudes in the left FDI when a compatible, incompatible or neutral word was presented and corticospinal excitability was assessed 250, 320, 500, or 640 msecs after word onset. The right line graph shows the raw MEP amplitudes for the right FDI when a compatible, incompatible or neutral word was presented and corticospinal excitability was assessed 250, 320, 500, or 640 msecs after word onset.

Discussion

There exists ample evidence for sensorimotor grounding of concrete action words and sentences (Aziz-Zadeh et al., 2006; Buccino et al., 2005; Hauk et al., 2004; Hauk & Pulvermüller, 2004; Tettamanti et al., 2005), for the influence of higher-order semantic classification on motoric components such as reaching and grasping kinematics (Gentilucci et al., 2000; Gentilucci & Gangitano, 1998; Glover & Dixon, 2002; Glover et al., 2005; Glover et al., 2004; Till et al., 2014), and for an interaction between location information and processing of spatial semantic categories (Luo & Proctor, 2013; O'Leary & Barber, 1993; Seymour, 1973). The current results add to these findings by providing the strongest evidence so far that the processing of the abstract, spatial concepts 'left' and 'right' is associated with activation (i.e. motor cortex excitability) in sensorimotor systems – when critically no overt response was required. To our knowledge, this is the first time that motor activation on the basis of abstract spatial information has been demonstrated at the level of M1 when response execution and response competition driven by multiple and potentially incompatible stimulus-features is prevented. Our results strengthen the weakest empirical link of the embodied cognition perspective by supporting the notion that even abstract spatial concepts are grounded in sensorimotor systems. According to dis-embodied views on cognition, abstract spatial concepts should not activate the sensorimotor system when no

further response is required, and this is clearly not what we observed here.

Showing M1 activation based on the processing of the words left and right is an important step towards a successful defense of the embodied perspective. Yet, one may argue that the activation is a non-critical side-effect of this processing and thus does not entail a true indication of grounding. (Pulvermüller, 2005) describes three criteria for demonstrating grounded cognition. The first criterion is speed. The observed effects should be fast. In the current study, TMS stimulation was executed as early as 250 (to 640) msecs after word onset, and an effect of compatibility on hemisphere-specific motor activation was observed independent of TMS timing. This suggests a fast modulation of corticospinal excitability by abstract, spatial and semantic information and thus confirms the first criterion by Pulvermüller (2005). However, whether comparable effects on corticospinal excitability could be observed when TMS stimulation was implemented at earlier intervals needs yet to be determined.

Second, the effect should be somatotopic. Translated to our context, this criterion entails that a lateral, hemisphere-specific effect should be observed in the sense that the word left (right) results in right(left) M1 motor activation. This criterion was confirmed in current study. Specifically, the results indicate that the perception and semantic interpretation of spatial information can lead to selective activation of M1. Larger stimulus-induced corticospinal excitability has been obtained on compatible trials for the

corresponding M1, while corticospinal excitability was significantly smaller when the semantics of the spatial stimulus did not correspond with the effector location (i.e. hemisphere-specific motor activation). Thus, the somatotopic criterion by Pulvermüller (2005) is also met.

Third, the activation should be automatic. In the current context this demands that focused attention towards the semantic feature of the stimulus is not required to execute the task and thus to generate sensorimotor cortex activation. In our experiment, the semantic stimulus does not hold any task-relevant feature to respond to, and thus no feature that requires focused attention. Indeed, already its mere surface features (shape, color, et cetera) are fully informative about the fact that on this trial no response is required. This satisfies the third criterion by Pulvermüller (2005). One may object that in our design, half of the trials required a left-right discrimination on the basis of the color of centrally presented circles, and this may have resulted in systematic pre-stimulus preparation of both response alternatives. This is perhaps true, but our main point is that we observed an asymmetrical increase of activation post-stimulus onset for one of two response alternatives based on the spatial word, which is difficult to explain based on (symmetrical) pre-stimulus preparatory mechanisms only. Overall we believe that the current results can be taken to indicate grounding of abstract spatial concepts in the sensorimotor system.

Furthermore, results show that the amplitude of MEPs decreases with increasing TMS latency. In general, it has been observed that response inhibition is associated with a decrease of MEP amplitude (van den Wildenberg et al., 2010). Moreover, this decrease of amplitude is contingent on the latency of the TMS pulse (Yamanaka et al., 2002). In line with these studies, we interpret our finding of a main effect of TMS latency as depicting response inhibition after the individual realized that he/she does not have to respond on the current trial. Consequently, corticospinal excitability and MEP amplitude decreases. Importantly, this decrease is observed irrespective of the stimulus. The selective motor excitability does not depend on time, in the sense that there is no interaction between the factors timing and compatibility.

The intermixing of color trials served a clear purpose in our study. On the basis of previous work (Ansorge & Wühr, 2004, 2009; Hommel, 1996; Wühr & Ansorge, 2007; Zhao et al., 2010) we predicted that without those trials, no motor activation would have been observed because this requires response discrimination in working memory. For instance, in a series of experiments, Ansorge and Wühr (2009) observed a Simon effect in a go/no-go task (requiring unimanual detection responses in go-trials) only when it was preceded by a choice-response task and when both tasks shared stimulus-response mappings. Conversely, before the choice-response task there was no reliable Simon effect in the go/no-go task. The Simon effect in the former case was assigned to a transfer of the required

response discrimination in working memory from the choice-response to the go/no-go task. Based on this type of finding, we decided to include the color trials to induce response discrimination in our participants. However, our design provides a strong paradigm to further test the notion of response discrimination. It would certainly be interesting to examine whether the processing of abstract spatial concepts modulates hemisphere-specific corticospinal excitability without the implementation of bimanual responses that need to be discriminated along a spatial axis. For instance, what would we observe if we delete the color-trials all together, and just let participants passively watch the spatial concepts be presented? More intermediate steps to examine the (unconditional) nature of embodiment of abstract spatial concepts may also be interesting. For example, one may ask individuals to respond to the color of stimuli via spatially defined, verbal responses (e.g. green circle, say 'right'). In this scenario, the individual effectively only distinguishes between spatial categories vocally and need not rely on bimanual right/left motor discriminations. If in this scenario similar MEP modulation is observed, this would hint at the possibility that a semantic (instead of a motoric) discrimination between (response) location alternatives may already be sufficient – broadening the perspective to a cognitive discrimination account. Hence, the current design has great promise for future exploration of issues related to automaticity. One may also argue that in the current study the color trials are only indirectly linked to spatial response

discrimination, because color stimuli did not inherently contain spatial (i.e. lateralized) properties. It could therefore also be interesting to examine the impact of spatial stimuli without spatial responses on the automatic motor activation as we observed it. More specifically, one could introduce lateralized stimuli and ask individuals to respond verbally in a non-lateralized fashion (e.g. left circle, say boo) while intermixing these trials with word trials. In this setup and according to the response-discrimination account, we would assume not to find the effects observed in the current study, because responses do not need to be distinguished along a spatial axis anymore.

Based on the three criteria pinpointed by Pulvermüller (2005), the current study fits the notion of grounded representation of abstract spatial concepts. Several cognitive frameworks have been introduced to substantiate the mechanisms underlying such grounded cognition. For example, Barsalou and Wiemer-Hastings (2005) proposed that abstract concepts are instantiated by the simulation of concrete situations to which the abstract concept applies. Thus, abstract concepts could (partly) be grounded in sensorimotor systems because they evoke simulation of concrete situations. However, the simulation of concrete versus abstract stimuli differs in terms of focal content. The content of abstract concepts is less focal because there are numerous concrete situations upon which the stimulations could be based. The broader representation of abstract concepts may therefore be associated with

distributed and more complex representations at the brain level (Pexman, Hargreaves, Edwards, Henry, & Goodyear, 2007) and may vary depending on contextual and situational constraints (Hoenig, Sim, Bochev, Herrnberger, & Kiefer, 2008). This framework of instantiating abstract concepts via simulation is coherent with studies that have shown that individuals are better in comprehending abstract material, when a linguistic context was provided compared to when the abstract material was presented in isolation (Schwanenflugel & Shoben, 1983). In current study, the concrete context may serve as anchor on which simulation is based. Thus, the implementation of right/left categories during color trials may provide the specific context where individuals could base their simulations upon.

Alternatively, the grounding-by-interaction framework (Mahon & Caramazza, 2008) suggests that sensory and motor information is important to provide an enriched context for conceptual processing. Instantiating abstract concepts is linked to the reactivation of sensory and motor information and would thereby ground conceptual representations in the sensorimotor system. In contrast to Barsalou and Wiemer-Hastings (2005) who are not specific about the consequences if individuals are unable to simulate concrete situations (e.g. apraxic patients), Mahon and Caramazza (2008) proposed that when conceptual processing would lack motor and sensory information, concepts would severely be impoverished but they would continue to exist in this impoverished form. Thus,

although conceptual representations can be generalized and are flexible in the sense that they can be applied to numerous concrete situations, information from sensorimotor (i.e. concrete) systems may provide a richer environment to better process conceptual representations.

Present results could be explained in line with the assumption that abstract concepts may benefit from simulating concrete situations. During half of the trials, individuals needed to discriminate between response alternatives and, therefore, needed to distinguish between spatial categories (i.e. left and right). During word trials, this discrimination may have served as concrete situation on which simulations of abstract spatial words (left and right) was based upon. Thus, without color trials, simulating a concrete situation in which the spatial categories left and right are of relevance and are linked to sensorimotor experiences may be more difficult.

One limitation of current study may be the choice for the abstract spatial concepts 'left' and 'right'. These concepts are surely abstract and spatial in themselves because they are not, for instance, spatially constraint or purely physically defined {Barsalou, 2005 #869}. However, the implementation of these concepts is often required in daily life. For instance, when a person looks for a specific product in the supermarket and is told that the product is to the left, the individual needs to implement the concept left (right) in order to find the product she is looking for. Correspondingly, the frequency

with which this spatial concept is motorically implemented in daily life may strengthen the concept-sensorimotor activation link and may shift abstract spatial concepts towards a more concrete interpretation with accompanying activation in sensorimotor brain regions. Alternatively, this spatial concept may easier be implemented than other abstract concepts (e.g. truth, freedom) due to the sheer number of available situations where this concept is implemented on a daily basis. Thus, spatial abstract information such as left (right) may have a processing advantage over other abstract concepts (e.g. freedom, truth) and may be accompanied by improved or heightened sensorimotor activation.

In conclusion, our results suggest that incidental processing of abstract spatial concepts is reflected in effector-specific M1 activation even though no response is required. These findings are coherent with the view that abstract concepts may be instantiated by simulating concrete situations and add to the discussion of sensorimotor grounding of abstract concepts.

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CHAPTER 3

REWARD ANTICIPATION MODULATES PRIMARY MOTOR CORTEX EXCITABILITY DURING TASK PREPARATION[1]

Task preparation has been associated with a transient suppression of corticospinal excitability (CSE) before target onset, but it is an open question to what extent CSE suppression during task preparation is susceptible to motivational factors. Here, we examined whether CSE suppression is modulated by reward anticipation, and, if so, how this modulation develops over time. We administered a cue-target delay paradigm in which 1000 ms before target onset a cue was presented indicating whether or not reward could be obtained for fast and accurate responses in a Simon task. Single-pulse transcranial magnetic stimulation was applied over left primary motor cortex (M1) during the delay period (400, 600, or 800 ms after cue onset) or 200 ms after target onset, and electromyography was obtained from the right first dorsal interosseous muscle.

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[1] Bundt, C., Abrahamse, E. L., Braem, S., Brass, M., & Notebaert, W. (2016). Reward anticipation modulates primary motor cortex excitability during task preparation. *Neuroimage, 142*, 483-488.

Behaviorally, the anticipation of reward improved performance (i.e. faster reaction times). Most importantly, during reward anticipation we observed a linear decrease of motor evoked potential amplitudes that was absent when no reward was anticipated. This suggests that reward anticipation modulates CSE during task preparation.

INTRODUCTION

By anticipating what is to come, task preparation allows humans to rapidly and flexibly meet environmental demands and plan actions (Bode & Haynes, 2009; Brass & Von Cramon, 2002, 2004). For example, in waiting at a crossroad for the traffic light to turn green, we monitor both the light and ongoing traffic, and prepare ourselves to switch gears and hit the gas when appropriate. In general, this type of task preparation can be divided into at least two main components: Configuring the attentional set in order to attend to the relevant information in the environment (e.g., monitor the light), and activating the relevant stimulus-response mappings to respond rapidly to the selected information (e.g., hold the gear stick).

An increasing number of studies have demonstrated that task preparation is sensitive to the anticipation of reward (for recent reviews, see Botvinick & Braver, 2015; Notebaert & Braem, 2015). However, all these studies focused on the first component of task preparation, demonstrating how the anticipation of reward can modulate preparatory attentional processes by increasing perceptual sensitivity to identify targets (Engelmann, Damaraju, Padmala, & Pessoa, 2009; Engelmann & Pessoa, 2014) or by improving the suppression of task-irrelevant information (Padmala & Pessoa, 2011). In contrast, the present study set out to investigate to what extent the second component, preparing the motor system for what is to come, might also be sensitive to motivational factors.

Recent studies using transcranial magnetic stimulation (TMS) in combination with electromyography (EMG) implicate the primary motor cortex (M1) in the preparation of the motor system. Specifically, the preparation of motor responses has been associated with decreased corticospinal excitability (CSE) (Duque & Ivry, 2009; Duque, Labruna, Verset, Olivier, & Ivry, 2012; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010; Greenhouse, Sias, Labruna, & Ivry, 2015; Lebon et al., 2015). For example, after cueing which effector (i.e., hand) would be involved in the response, Duque and Ivry (2009) reported a most prominent pre-stimulus decrease in CSE for the hand involved in the forthcoming response execution. Furthermore, decreased CSE has also been found when participants could not anticipate the forthcoming response (Duque & Ivry, 2009), and for task-irrelevant and non-homologous muscles (Greenhouse et al., 2015). Consequently, it has been suggested that preparatory CSE suppression reflects a general mechanism that prepares for multiple potential actions by suppressing the whole motor output system during task preparation (Cisek, 2007; Cisek & Kalaska, 2005; Koch et al., 2006). Accordingly, a continuous tug-of-war between distinct action representations in the motor cortex is assumed to reflect the impact of multiple (cognitive) processes biasing the system towards an action alternative (i.e. preparation to act), implemented by a parallel flow of information between perceptual decision making systems and the motor system (Bestmann & Duque, 2016; Cisek, 2012; Servant, White, Montagnini, & Burle, 2015; Thura & Cisek, 2014).

Hence, CSE suppression might be an important aspect of action selection. If the latter is indeed the case, we expect it to be modulated by motivational factors.

Various studies have investigated the impact of motivation on CSE prior to action execution (e.g. Chiu, Cools, & Aron, 2014; Gupta & Aron, 2011; Suzuki et al., 2014; Vassena, Cobbaert, Andres, Fias, & Verguts, 2015). In these studies, however, (partial) information about which action to perform was provided before excitability was measured. These studies generally observed that higher states of motivation (e.g. after the anticipation of affective or reward predicting stimuli compared to aversive or no reward predicting stimuli) were associated with increased CSE. This approach certainly yields insight into the effects of motivation on CSE when preparing specific actions, but does not provide information about a general, task-preparatory effect at play when no information about the required response is provided. In the present study, we investigated whether task-preparatory, pre-target motor suppression is modulated by reward anticipation, and if so, how this motivational influence develops over time. Contrary to earlier studies investigating motivational effects on CSE, we measured motor evoked potentials (MEPs) before any information about the target was available. We presented reward cues one second before target onset. The cue indicated whether reward could be obtained or not after good performance (see below). Within the cue-target delay period, we applied single-pulse TMS over the left M1 to probe CSE

during one of three different epochs (400, 600, or 800 ms after cue onset), while EMG was recorded from the right first dorsal interosseous (FDI). Besides the impact of reward anticipation on motor suppression, a secondary aim of the current study was to explore the relationship between reward anticipation and conflict behaviorally and at the neurophysiological level. To this end, targets consisted of lateralized, colored circles (i.e. Simon stimuli) and participants were instructed to respond to the color of the target by providing a left or right index finger response. We chose to administer a Simon task to investigate whether, much like the reduced interference effect in Stroop-like paradigms (Padmala & Pessoa, 2011), reward anticipation would also attenuate the well-known Simon effect (faster responses when stimulus location corresponds spatially with response location; Simon, 1969). Additionally, previous investigations have shown that at the neurophysiological level the task-irrelevant location of (incompatible) Simon stimuli evoked an early transient increase of CSE in the uninvolved hand, followed by a continuous CSE increase in the involved hand, suggesting that the canonical behavioral Simon effect could be traced back to alterations in CSE (van Campen, Keuken, van den Wildenberg, & Ridderinkhof, 2014). However, evidence that conflict in the Simon task may interact with reward anticipation at the level of M1 is limited (c.f. Herz et al., 2014). Correspondingly, a fourth potential stimulation epoch was added in which a TMS pulse over left M1 could be applied 200 ms after target

onset to investigate the consequences of conflict and reward anticipation on CSE.

METHODS

Participants

Twenty right-handed participants (sixteen female, M = 22.6 years, SD = 2.3 years) were naïve to the real purpose of the study and prescreened for psychiatric and neurological disorders as well as for factors that may interfere with a safe application of TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Participants provided written informed consent and were monetarily compensated (30€). Furthermore, prior to the experiment, they were informed that the best-performing participant would receive a voucher (25€) for a multimedia store. The study was approved by the ethical committee at the Ghent University Hospital.

TMS stimulation and EMG recordings

EMG was measured from the right FDI muscle that is crucial for abducing the right index finger away from the right middle finger. An ActiveTwo system (www.biosemi.com) was used to record EMG activity, while sintered 11 × 17 mm active Ag-AgCl electrodes were mounted on the right FDI and on the metacarpophalangeal joint, respectively. Two ground-electrodes were placed on the dorsum of the hand. The EMG signal was amplified via internal gain scaling, digitized at 2048 Hz and high-pass filtered at 3 Hz.

Primary motor cortex was stimulated using a 70 mm figure of eight coil connected to a biphasic stimulator (Rapid2; The Magstim

Company Ltd.) (for recent reviews, see Bestmann & Duque, 2016; Bestmann & Krakauer, 2015). The stimulation coil was tangentially positioned over the right hand motor area (i.e. left M1) so that the handle pointed to the dorsocaudal part of the participant's head, thereby creating an angle of 45° with the sagittal plane. The coil was held by a mechanical arm throughout the experiment. The TMS stimulation location was determined by the scalp position that evoked the most reliable MEP. Throughout the whole experiment, participants wore a swimming cap where the optimal stimulation location was marked. Correspondingly, the experimenter could continuously monitor TMS stimulation location. The resting motor threshold (rMT) was dependent on the stimulation intensity that evoked MEPs larger than 50 μV in 50% of the cases (Rossini et al., 1994). Eventual stimulation intensity was adjusted to 110% of the rMT. On average, this led to a stimulation intensity of 62% (range 43% - 78%) of the maximal stimulator output.

Stimuli and procedure

Participants were seated in a comfortable chair with an eye-monitor distance of approximately 50 centimeters. Participants were instructed to place their tips of their left and right index finger on a reversed QWERTY keyboard between the F4, F5 and F8, F9 buttons respectively (cf. Klein, Olivier, & Duque, 2012). Moreover, they were asked to respond with an abduction movement towards the medial response buttons (F5 and F8) to eventually perform a key press.

Stimulus presentation was carried out by Presentation® software (Version 16.3, www.neurobs.com) on a 17-inch computer monitor (1024 × 768 pixels).

Individuals were able to accumulate points for fast and accurate responses on 50% of all trials. Fast and accurate responses were predefined as correct responses that occur within 700 ms after target onset. Thus, if individuals accurately responded within 700 ms after target onset on reward trials, they earned an additional point. However, if they responded slower than 700 ms they did not receive any points on that trial. Participants were told that they could win a voucher for a local multimedia store when they accumulated the highest amount of points across all participants.

Each trial began with the presentation of a fixation star for 500 ms. Thereafter, a cue was presented above the fixation that indicated whether subjects could obtain reward for fast and accurate responses or whether no reward could be obtained on the current trial (see Fig. 1 for a schematic illustration of the trial procedure). More specifically, a '+1' presented above fixation was indicative of potential reward, whereas a '+0' indicated no reward. Both the cue and fixation star were presented for 300 ms. This was followed by a fixation period for 700 ms. Within this interval, during 60% of the trials, CSE was assessed 400, 600 or 800 ms after cue onset (i.e. 100, 300, 500 ms after cue offset). Subsequently, a colored circle (i.e. Simon stimulus) was presented left or right of fixation for maximally 1000 ms. Depending on the color of the circle, participants were required to respond with

a left/right FDI abduction movement towards and eventually press the response key. During another 20% of the trials, a TMS pulse was applied over the left M1 200 ms after target onset to examine CSE during task processing. Last, during the remaining 20% of the trials, no TMS stimulation was applied. If participants responded within the 1000 ms window of stimulus presentation a fixation period followed for 200 ms. Eventually, a feedback screen was shown for 1000 ms. Specifically, on reward trials, if participants provided a correct response within the allowed time window after target onset, this feedback screen consisted of either '+1' (if the response was provided within 700 ms after target onset) or '+0' (if the response was provided between 701-1000 ms after target onset) presented above fixation; hence, these feedback screens indicated that the participant obtained a reward or not, respectively. On no-reward trials, feedback consisted of only '+0' presented above fixation, irrespective of response time as participants could not earn any points on these trials. If participants did not respond correctly or within the time limit, the string "wrong" or "too late" was displayed above fixation. Below fixation, the total amount of reward was always displayed. Trials were separated by a jittered inter-trial-interval of 1100 to 1300 ms.

Participants completed 800 trials divided across ten experimental blocks of 80 trials each, which were separated by a pause of 30 seconds. The experiment consisted of an equal amount of randomly presented trials, balanced across responses (left/right FDI),

compatibility, (no) reward, and (no) TMS epochs. In total, participants took around 75 minutes to complete the experimental session.

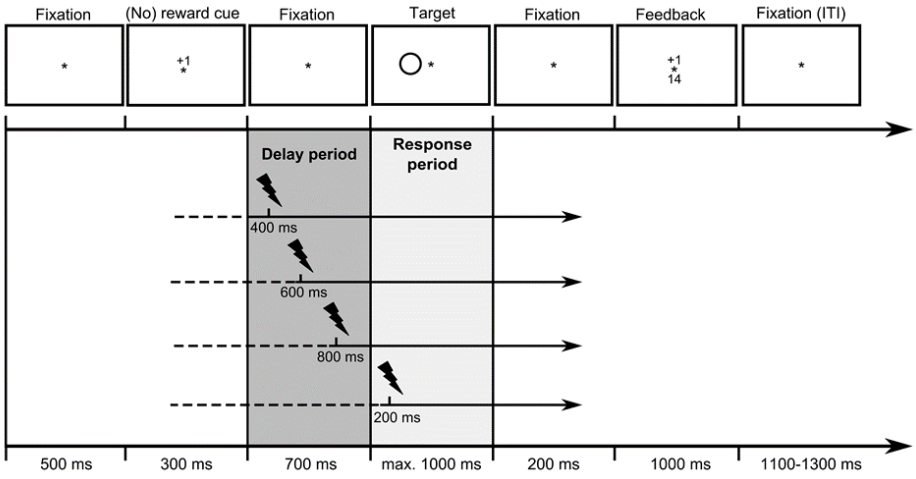

Fig. 1. Schematic illustration of the experimental trial procedure. Each trial began with a fixation period of 500 ms. Thereafter, a (no) reward cue ("+0" or "+1") was presented (300 ms), followed by a delay period (700 ms) and the presentation of the target (max. 1000 ms). After subjects provided a response during target presentation, a short fixation period (200 ms) was followed by feedback (1000 ms) and a jittered inter-trial-interval (ITI; 1100 – 1300 ms). Maximally one TMS pulse was applied per trial: at 400ms, 600 ms, or 800 ms after cue onset, or 200 ms after target onset. Twenty percent of all trials did not include TMS. Erroneous responses and response omissions were communicated to the subject on screen.

Data analysis: behavior

Since TMS stimulation may interfere with behavioral performance (Hasbroucq, Kaneko, Akamatsu, & Possamaï, 1997), only trials where no TMS stimulation was applied were included for behavioral data analyses. Trials with premature responses (<100 ms) or response omissions (>1000 ms), and trials that followed an incorrect response were excluded from further analyses. Both correct RTs and percentage correct trials were submitted to a repeated-measures ANOVA (RMANOVA) with reward (reward, no reward) × compatibility (compatible, incompatible) as within-subject factors.

Data analysis: CSE

For each valid trial, the peak-to-peak amplitude of the MEP was calculated. First, EMG epochs starting 500 ms before and ending 500 ms after the actual event (i.e. the TMS pulse) were extracted from the recorded data. Trials were checked for background EMG activity during a time window of 500 ms preceding the TMS pulse. The trial was rejected if the root mean square of the background EMG activity was larger than 100 μV during this window. The MEP amplitude was calculated for the 20-40 ms window following a TMS pulse (i.e. this is the typical time range at which a MEP occurs) using MATLAB® software. Additionally, trials where responses occurred <100 or >1000 ms after target onset, trials with responses provided before or during the TMS pulse as well as trials with incorrect responses, and trials that followed an incorrect response on previous trial were omitted

from the analysis. Moreover, we excluded trials where the MEP amplitude was above or below three standard deviations from the individual MEP mean (for each MEP analysis respectively).

For the remaining trials, a Z transformation was applied to the MEP data (Burle, Bonnet, Vidal, Possamai, & Hasbroucq, 2002; van den Wildenberg et al., 2010). More specifically, the mean and standard deviation was calculated for each subject and condition that were used for the same analyses (i.e. separate Z transformation for delay period and target CSE analysis). Then for each subject, a Z score was computed by subtracting the overall trial population mean from the individual trial MEP and dividing it by the standard deviation of the trial population. Thereafter, these Z scores were averaged and submitted to RMANOVAs (see below).

To inspect the reward-driven changes in M1 during motor-related task preparation within the delay period, electrophysiological data was submitted to a 2 × 3 RMANOVA with cue (reward, no reward) × timing (400, 600, 800 ms) as within-subject factors. In order to investigate the effect of reward on response execution, a 2 × 2 × 2 RMANOVA with involvement (involved hand, uninvolved hand) × reward (reward, no reward) × compatibility (compatible, incompatible) as within-subject factors was performed on the MEP data. The factor involvement indicates whether the right hand (where we measure the MEPs) was required for the correct response or not. Statistical analyses were performed using SPSS (Version 22.0. Armonk, NY, USA: IBM Corp.). Statistical significance thresholds

were set to $p = 0.05$ and when necessary, Greenhouse-Geisser epsilon was applied.

RESULTS

Behavior

Individuals were faster to respond to targets after a reward cue than after a no-reward cue (540 ms vs. 555 ms) ($F(1,19) = 13.602$, $p = 0.002$, $\eta p^2 = 0.417$). Moreover, individuals were faster to respond to compatible than to incompatible targets (534 ms vs. 560 ms, indicating a Simon effect of 26 ms, ($F(1,19) = 52.721$, $p < 0.001$, $\eta p^2 = 0.735$) (Fig. 2A). There was no interaction between reward and compatibility ($F(1,19) < 1$, $p = 0.996$), indicating that the Simon effect was similar after reward and no-reward cues.

In error rates, there was no effect of reward, ($F(1,19) = 2.108$, $p = 0.163$, $\eta p2 = 0.100$). There was a Simon effect in accuracy ($F(1,19) = 9.228$, $p = 0.007$, $\eta p^2 = 0.327$), illustrating higher accuracy on spatially compatible trials compared to incompatible trials (99% vs. 97%) (Fig. 2B). There was no interaction between reward and compatibility ($F(1,19) < 1$, $p = 0.892$, $\eta p^2 = 0.001$).

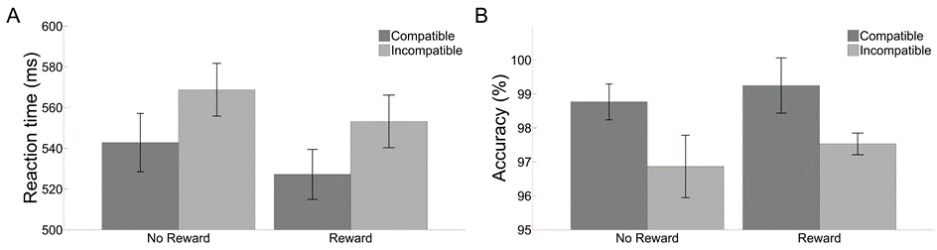

Fig. 2. Behavior. Mean reaction time (A) and accuracy (B) during non-pulse trials depicting compatibility (compatible vs. incompatible) and motivational cue (no reward vs. reward). Bars indicate one standard error.

CSE

The analysis on raw MEP versus Z-transformed values yielded comparable effects, and we therefore decided to report statistics for Z-transformed values only. The analysis of CSE during the delay period revealed no main effect of reward ($F(1,19) = 0.136$, $p = 0.716$, $\eta p^2 = 0.007$) but a main effect of timing ($F(2,38) = 4.236$, $p = 0.022$, $\eta p^2 = .182$). Most important, there was an interaction between reward and timing ($F(2,38) = 5.695$, $p = .007$, $\eta p^2 = 0.231$) (Fig. 3). The interaction, depicted in Figure 3, can most clearly be captured in terms of slopes. We therefore calculated the slope for each participant and tested whether the average slope differed significantly from zero. This analysis revealed that after a reward cue, there was a linear increase of CSE suppression, ($t(19) = -4.005$, $p = 0.001$), which was not observed after a no-reward cue ($t(19) = -0.067$, $p = 0.947$).

Figure 3 suggests CSE differences during the first (400 ms) and last (800 ms) TMS epoch and no differences during the intermediate (600 ms) TMS epoch between (no) reward trials. Paired sample t tests (two-tailed) revealed a marginally significant effect for the first TMS epoch (400 ms; $t(19) = -2.054$, $p = 0.054$), no effect for the intermediate TMS epoch (600 ms; $t(19) = 0.245$, $p = 0.809$), and a significant effect for the last TMS epoch (800 ms; $t(19) = -2.242$, $p = 0.037$).

In order to measure the correlation between the behavioral and the corticospinal suppression effect, we calculated two indices for each participant. The behavioral reward effect is the RT benefit for reward trials (RT no-reward – RT reward), while the corticospinal effect was considered as the individual difference between the slope of the reward trials and the slope of the no-reward trials. This correlation turned out not significant ($r = 0.377$, $p = 0.101$).

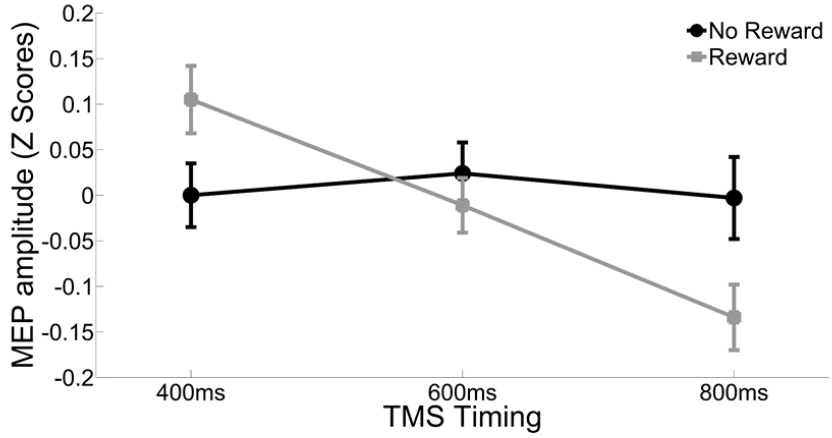

Fig. 3. Delay period CSE. Mean normalized MEP amplitude for each TMS stimulation epochs (400 ms, 600 ms, 800 ms after cue onset) and motivational cue (no reward, reward) during the delay period. Bars indicate one standard error.

After target onset, there was no main effect of reward ($F(1,19)$ = 2.289, p = 0.147, ηp^2 = 0.108), and no effect of involvement ($F(1,19)$ = 0.292, p = 0.595, ηp^2 = 0.015). However, there was a Simon effect in the sense that compatible trials lead to increased excitability ($F(1,19)$ = 4.441, p = 0.049, ηp^2 = 0.189).

There was a trend towards an interaction between involvement and reward ($F(1,19)$ = 3.164, p = .091, ηp^2 = 0.143) tentatively suggesting higher CSE when the hand was involved (i.e. required for the current response) relative to when it was not involved during reward trials,

while this pattern seemed to be less prominent during no-reward trials (both paired-sample t tests *p*s > 0.2 however).

Last, there was no interaction between involvement and compatibility ($F(1,19) = 0.204$, $p = 0.657$, $\eta p^2 = 0.011$), and between reward and compatibility ($F(1,19) = 0.962$, $p = 0.339$, $\eta p^2 = 0.048$). The three-way interaction was not significant ($F(1,19) = 1.002$, $p = 0.329$, $\eta p^2 = 0.050$). Note, that CSE will be higher closer to the response. Therefore, increased CSE for reward and compatibility (factors that also influence RT) should be interpreted with caution. To investigate this, a linear regression analysis was performed on MEPs with the predictors involvement, reward and compatibility, their respective interaction terms as well as reaction time. This analysis revealed that MEPs were significantly predicted by reaction time ($p = .019$) but also by congruency ($p = .039$), emphasizing that CSE changes following target onset were partially associated with behavioral performance variability and, therefore, need to be interpreted cautiously.

DISCUSSION

The current study examined the influence of reward on (nonspecific) motor-related task preparation. The main results showed a reward-specific continuous decrease of MEPs during task preparation peaking just before target onset. In comparison, the anticipation of a no-reward trial did not change MEPs over the different TMS stimulation epochs.

Relative CSE suppression has been found during action preparation to meet environmental demands (Duque & Ivry, 2009; Duque et al., 2010; Greenhouse et al., 2015; Lebon et al., 2015), even when it was impossible to anticipate specific forthcoming responses (Duque & Ivry, 2009), and for task-irrelevant and non-homologous muscles (Greenhouse et al., 2015). This is in line with the view that a broad cognitive mechanism prepares for multiple potential actions (Cisek & Kalaska, 2005; Koch et al., 2006). Moreover, there is growing evidence for the notion that motivational aspects affect M1 (Chiu et al., 2014; Freeman & Aron, 2016; Gupta & Aron, 2011; Kapogiannis, Campion, Grafman, & Wassermann, 2008; Klein-Flügge & Bestmann, 2012; Klein et al., 2012; Suzuki et al., 2014; Thabit et al., 2011; Vassena et al., 2015). Yet, the current study is the first to unambiguously demonstrate that task preparation as reflected in relative CSE suppression is modulated by reward anticipation in a time-dependent manner (i.e., stronger MEP decrease close to target onset during the expectation of potential reward compared to no reward).

Response preparation by means of CSE suppression may be tentatively linked to either of two functional mechanisms: impulse control or competition resolution (Duque et al., 2012; Duque et al., 2010). Impulse control reflects an inhibitory mechanism that is crucial for avoiding premature responses, whereas competition resolution is associated with the concurrent (de-)activation of (in-)correct responses (Duque et al., 2010).

Impulse control has recently been associated with dorsal premotor cortex (PMd) functionality. By combining repetitive TMS with single-pulse TMS, Duque et al. (2012) showed that in a cued choice reaction time task repetitive TMS over PMd decreased CSE inhibition in an effector selected for a forthcoming response, whereas repetitive TMS over lateral prefrontal cortex (LPFC) attenuated inhibition in both, selected and unselected effectors. These observations suggest that LPFC is involved in competition resolution between selected and unselected responses, whereas PMd is involved in impulse control (i.e. control over selected responses). Possibly in line with current results, PMd's role may be extended to a nonspecific generation of inhibitory signals over widely distributed brain regions in order to prevent premature action execution (Prut & Fetz, 1999). Interestingly, PMd receives major dopaminergic projections from the midbrain, and accommodates one of the highest amount of D1 dopamine receptors within the primate frontal cortex (Sawaguchi, 1997). Correspondingly, the differential reward-related effects of (no) reward anticipation during task preparation on CSE may be

mediated by PMd as target for dopaminergic projections (c.f. Ramnani & Miall, 2003). Thus, as no response was specified prior to target onset and therefore competition resolution mechanisms (between selected and unselected response options) are unlikely in the current task design, the observed cue-related decrease of CSE suggests general motor suppression (Cisek & Kalaska, 2005; Koch et al., 2006) that is predominantly related to impulse control and possibly mediated by a direct dopaminergic input from the midbrain to the PMd.

It is noteworthy that the interaction between reward and TMS stimulation epochs was partly due to a reward-related CSE increase (compared to no reward) during the first stimulation epoch (i.e. 400 ms). Although not predicted a priori, this initial reward-related relative CSE increase could reflect the influence of the reward cue triggering the tendency to perform approach/appetitive behavior towards this stimulus (Schultz, 2006; Schultz et al., 1998), thereby resulting in increased reward-related CSE early during motor preparation. In line with this interpretation, Chiu et al. (2014) investigated the influence of affective and aversive cues on CSE in a Go/NoGo task. In their study, Go/NoGo responses were determined by a combination of motivational (affective/aversive) and symbolic (triangle/rectangle) cues. Motivational and symbolic cues were presented successively but were separated by a delay period during which CSE was assessed (Exp. 2). Thus, during motivational cue presentation, individuals were not able to predict the correct

forthcoming response, because the symbolic cue was not presented yet. Interestingly, however, Chiu and colleagues reported that appetitive cues resulted in increased CSE, whereas aversive cues were associated with decreased CSE, although the actual response was unknown at the time of CSE examination. This finding suggests a fast, valence-dependent motivational effect on CSE. In line with these findings, we tentatively interpret the relative CSE increase for reward trials during the first TMS stimulation epoch as reflecting the tendency to perform approach behavior (see also Mooshagian, Keisler, Zimmermann, Schweickert, & Wassermann, 2015; Vassena et al., 2015).

In the current study, we did not observe a transient decrease of MEPs for no-reward trials (note, however, that we cannot exclude the possibility of de- or increased MEPs as we did not examine baseline CSE). This finding adds to a growing number of observations where the cognitive control effect of interest disappears following no-reward trials (for a review, see Notebaert & Braem, 2015). Accordingly, in the present study distinguishing between reward levels may have devaluated no-reward (i.e. neutral) trials resulting in no relative CSE change during no-reward trials. This finding suggests a dynamic stimulus (or trial) prioritization and emphasizes the role of intrinsic motivation in cognitive control (Satterthwaite et al., 2012; Schouppe et al., 2015).

In contrast to previous studies with Stroop tasks (Padmala & Pessoa, 2011; van den Berg, Krebs, Lorist, & Woldorff, 2014), we did not

observe a reduced behavioral Simon effect after a reward cue (c.f. Herz et al., 2014). Although surprising, this may be attributable to the finding that the Simon effect is largest for fast RTs, whereas the Stroop effect is known to increase over time (Pratte, Rouder, Morey, & Feng, 2010). Consequently, the Stroop task (compared to the Simon task) may offer more time for motivational modulations to come into effect, leading to reduced Stroop effects after reward. Nonetheless, although the interference effect was not modulated by reward anticipation in the Simon task, current results are in line with previous observations that proposed that reward may have a non-specific enhancing effect on performance (i.e. general speeding up of responses) (Niv, Joel, & Dayan, 2006; Wang, Miura, & Uchida, 2013). Although reward altered CSE and improved reaction times, there was no significant correlation between them. We are aware that the lack of a correlation warrants only limited conclusions, and this is especially the case for a correlation with a p-value of .10. Hence, on the basis of the current data, we cannot make claims on the relationship between reward-related speeding and reward-related CSE suppression.

In conclusion, current results suggest that reward anticipation affects motor-related task-preparatory mechanisms. This reward-related relative CSE suppression builds up over time and is strongest just before target onset, whereas the anticipation of no reward did not substantially modulate MEPs during task preparation. After target presentation, compatible stimuli were associated with relatively

larger MEPs, while incompatible stimuli were associated with relatively smaller MEPs. Our results suggest that motivation is a major modulator of effector-unspecific broad motor suppression.

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CHAPTER 4

REWARD DOES NOT ALTER CORTICOSPINAL EXCITABILITY DURING STROOP TASK PREPARATION

Action preparation has been linked to a transient corticospinal (CS) suppression before target onset. Recently, it was shown that reward anticipation modulates this preparatory CS suppression. In the present study, we examined reward-modulated preparatory CS suppression, and its functional role, in the Stroop task. We administered a rewarded cue-target delay paradigm, in which a reward (+1) or a non-reward (+0) cue was presented 1000 ms before target presentation for 300 ms, indicating whether or not a reward could be obtained for fast and accurate target performance, respectively. Single-pulse transcranial magnetic stimulation (spTMS) was administered over the left primary motor cortex (M1) at one of three different moments after cue onset during the delay period (400, 600, or 800 ms), or 200 ms after target onset, which could be referenced to a baseline stimulus preceding cue presentation. Electromyography (EMG) was obtained from the right first dorsal interosseous (FDI) muscle. Behaviorally, reward compared to non-reward anticipation decreased reaction times and improved accuracy. Furthermore, the behavioral congruency effect increased for reward compared to non-reward anticipation. In line with

previous findings, there was a preparatory linear increase of CS suppression throughout the delay period. However, preparatory CS suppression was not modulated by reward. These results suggest that a reward effect on the motor system may depend on task specifics and may not have an unconditional effect on the motor system.

INTRODUCTION

Task and response preparation is a fundamental ability that enables humans to meet environmental demands in a timely, accurate, and flexible manner (Bode & Haynes, 2009; Brass & Von Cramon, 2002, 2004). Using transcranial magnetic stimulation (TMS) and concurrent electromyography (EMG), studies have linked corticospinal (CS) excitability to action preparation (Duque & Ivry, 2009; Greenhouse, Sias, Labruna, & Ivry, 2015; Lebon et al., 2015). Strong CS suppression has been observed during the preparation of a forthcoming response for selected responses (Duque & Ivry, 2009). However, CS suppression has also been found for responses that could not be anticipated (e.g., when the response selection still had to be made; Bundt, Abrahamse, Braem, Brass, & Notebaert, 2016; Duque & Ivry, 2009), and for task-irrelevant muscles (Greenhouse et al., 2015). CS suppression may therefore represent a broad and effector-unspecific mechanism that enables individuals to prepare multiple potential actions (Cisek, 2006, 2007). To determine the most relevant action, it is assumed that various processes and regions bias the "tug-of-war" between distinct action representations in a parallel and continuous fashion (Bestmann & Duque, 2016).

The application of TMS over motor areas (typically over primary motor cortex (M1)) provides a temporally precise readout of the state of the motor system, reflecting a net outcome of the distinct processes that underlie the dynamic competition between different

action representations during action preparation (Bestmann & Krakauer, 2015). In recent years, effort has been made to disentangle these individual factors and processes biasing the motor system towards a response alternative during action preparation. These attempts have revealed, for example, that the motor system is biased by decision-related variables such as the estimation of biomechanical costs (Cos, Duque, & Cisek, 2014) and subjective value (Klein-Flügge & Bestmann, 2012) associated with response alternatives. Importantly, it has also been shown that reward dynamically biases the motor system during action preparation (e.g., Chiu, Cools, & Aron, 2014; Gupta & Aron, 2011; Suzuki et al., 2014; Vassena, Cobbaert, Andres, Fias, & Verguts, 2015). These studies have shown that the reward compared to non-reward anticipation resulted in relatively increased CS excitability (Chiu, Cools, & Aron, 2014; Gupta & Aron, 2011), higher probability of reward delivery led to relatively decreased CS excitability before a manual response (Suzuki et al., 2014), and that the effect reward has on the motor system may depend on the level of effort incurred by the task (Vassena et al., 2015). However, these studies (if at all) examined response-specific motor preparation only (i.e., the forthcoming response was (partially) defined before CS excitability was measured).

To examine motivational effects on general action preparation (i.e., prior to response selection) we recently devised a cue-target delay paradigm in which a "+1" or a "+0" cue was predictive of whether or not a reward could be obtained for fast and accurate target

performance, respectively (Bundt et al., 2016). Importantly, cue presentation was followed by a delay period in which CS excitability was assessed during three equally distributed moments, before the target was presented. We found that on reward compared to non-reward anticipation trials there was an initial CS excitability increase followed by a sharp decrease that resulted in relative CS suppression just before target onset. These results suggested that reward invigorates (general) action preparation.

The present study set out to substantiate previous findings but changed the previous design in two important ways. First, in the previous study it was impossible to determine whether non-reward anticipation was associated with actual CS suppression as there was no baseline measurement of CS excitability (for a discussion on the interpretability of TMS baseline measures, see Bestmann & Krakauer, 2015). In the present study, a baseline TMS pulse was applied 200 ms before reward-cue presentation, allowing us to examine CS changes relative to baseline. Second, while in the previous study we used a Simon task, we now turn to the Stroop task. In this earlier work, we observed no modulation of the size of the Simon effect (i.e., reaction time or accuracy difference between ingongruent and congruent stimuli) by the reward manipulation (Bundt et al., 2016) while previously, this was demonstrated for the Stroop effect. More precisely, Padmala and Pessoa (2011) observed that reward reduces the interference (incongruent reaction times > neutral reaction times) and facilitation effect (congruent reaction

times < neutral Rreaction times) in a Stroop-like task, and Soutschek, Strobach, and Schubert (2014) reported a diminished Stroop effect in high-reward compared to low-reward blocks. However, a modulation of the Stroop effect by reward has not always been observed. van den Berg, Krebs, Lorist, and Woldorff (2014), for instance, employed a cue-target delay Stroop task in which an initial cue indicated whether participants could receive monetary reward upon sufficiently fast and correct target performance. In contrast to the studies mentioned before, van den Berg et al. did not find a modulation (i.e., reduction) of the behavioral Stroop effect during reward-prospect compared to non-reward-prospect. However, the authors reported a robust correlation across participants between the size of the Stroop effect and the size of the reward prospect effect (reward-prospect minus non-reward prospect), suggesting that when participants strongly utilize cue information, the Stroop interference effect is reduced.

Thus, evidence regarding a modulation of the Stroop effect by reward is still ambiguous. By means of the Stroop task, we intend to evaluate whether a modulation of the congruency effect (by reward) is related to CS suppression. After the pre-cue fixation period (potentially including a baseline TMS pulse) a (non-) reward cue was presented for 300 ms followed by a delay period of 700 ms. During the delay period, CS excitability was examined at one of three different moments (400, 600, or 800 ms after cue onset) by applying single-pulse TMS (spTMS) over left M1 to probe CS excitability during action preparation. Based on our previous research (Bundt et

al., 2016), we hypothesized that reward compared to non-reward anticipation results in an initial increase of CS excitability followed by a linear decrease of CS excitability resulting in stronger CS suppression just before target onset relative to non-reward anticipation(c.f., Bundt et al., 2016)(c.f., Bundt et al., 2016)(c.f., Bundt et al., 2016)(c.f., Bundt et al., 2016)(c.f., Bundt et al., 2016)(c.f., Bundt et al., 2016). After the delay period, the target (Stroop) stimulus was presented for maximally 1000 ms upon which individuals were required to provide a manual response with their left or right index finger. Furthermore, because evidence regarding a modulation of the Stroop effect by reward is ambiguous, we tentatively expected reduced behavioral congruency effects for reward compared to non-reward anticipation in accordance with previous findings (Padmala & Pessoa, 2011; Soutschek et al., 2014), suggesting that reward reduces interference and facilitation effects in a Stroop task (Padmala & Pessoa, 2011). Neurophysiological evidence using TMS to examine conflict in the Stroop task is rare. To explore the effect of Stroop conflict and reward on the motor system another TMS pulse could be applied 200 ms after target presentation (c.f., Bundt et al., 2016).

METHODS

Participants

Thirty-eight, right-handed individuals participated in this study (twenty-five female, M = 22.5 years, SD = 2.1 years). All participants were prescreened for neurological and psychiatric disorders and for factors that may interfere with a safe application of TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Individuals provided written informed consent and were monetarily compensated for their participation (25€). Additionally, and prior to the experiment, individuals were briefed that the best-performing participant could receive an additional bonus (25€ voucher for multimedia store; c.f., Bundt et al., 2016). The study was performed in accordance with the declaration of Helsinki and approved by the ethical committee at Ghent University Hospital.

TMS stimulation and EMG recordings

TMS stimulation and EMG recording procedures were identical to Bundt et al. (2016). The stimulation intensity was set to 110% of the resting motor threshold (rMT). On average, the stimulation intensity was M=66.8% ± SD=8% of the maximal stimulator output.

Stimuli and procedure

The experimental environment as well as stimuli presentation hard- and software was identical to Bundt et al. (2016). Participants could accumulate points for fast and accurate performance in 50% of all trials. Unbeknownst to the participants, fast and accurate performance was predefined as correct responses within 700 ms after target presentation on reward trials, upon which they received an extra point. Incorrect or slower responses were not rewarded with an extra point. The total amount of points an individual accumulated throughout the experiment was associated with the probability of the participant to receive an additional 25€ voucher for a multimedia store (i.e., the more points an individual had accumulated the higher the probability that (s)he received the extra 25€ voucher among all participants).

Each trial began with a (pre-cue) fixation asterisk presented for 500 ms in the center of the computer screen (see Fig. 1 for a schematic illustration of the experimental design). During this interval a baseline TMS pulse was occasionally applied 300 ms after fixation onset. Thereafter, a motivational (i.e., non-reward or reward) cue was presented above the fixation asterisk for 300 ms. The (non-) reward cue was either a printed "+0" or a "+1" indicating that no reward (+0) or reward (+1) could be obtained on the current trial for fast and accurate performance. After the presentation of the motivational cue, another fixation period followed for 700 ms (i.e., delay period) during which CS excitability could be assessed. TMS was applied during the delay period at three different moments (i.e., 400 ms, 600 ms, or 800 ms after motivational cue onset). Subsequently, Stroop color stimuli were presented above fixation for maximally 1000 ms. Stroop color stimuli were composed of the color words BLAUW, ROOD, GEEL, GROEN (Dutch for BLUE, RED, YELLOW, GREEN) either colored in the same (i.e., congruent Stroop stimulus; 50% of all trials) or in a different ink color (i.e., incongruent Stroop stimulus; 50% of all trials). Depending on the ink color of the Stroop stimulus (red and yellow ink-color was mapped on one response, whereas green and blue ink-color was mapped on the other), individuals were asked to respond via a left or right index finger abduction movement towards a medial response key and eventually press it (c.f., Bundt et al., 2016; Bundt, Bardi, Abrahamse, Brass, & Notebaert, 2015; Klein, Olivier, & Duque, 2012; Klein, Petitjean, Olivier, & Duque, 2014). On some trials, target

CS excitability was examined 200 ms after target stimulus onset to examine target-related state changes of the motor system. If individuals responded in time (i.e., within 1000 ms), target presentation was terminated after pressing the correct response key and another fixation period followed for 200 ms. Thereafter, feedback was presented for 1000 ms, which was comprised of the presentation of the points obtained on current trial above fixation, and the accumulated amount of points below fixation. Thus, on non-reward trials, the feedback always consisted of a "+0" above fixation indicative an unchanged total point score. However, on reward trials, if individuals responded correctly within 700 ms after target onset, feedback above fixation was "+1" indicative of an extra point earned on the current trial. If individuals, responded slower than 700 ms but within the allowed time window of 1000 ms on reward trials, the feedback was '+0' and thus no reward was obtained on current trial. If participants did not or responded incorrectly, a "te laat" (Dutch for "too late") or a "fout" (Dutch for "wrong") was displayed above fixation for 1000 ms. Trials were separated by a randomly jittered inter-trial-interval of 1100 to 1300 ms.

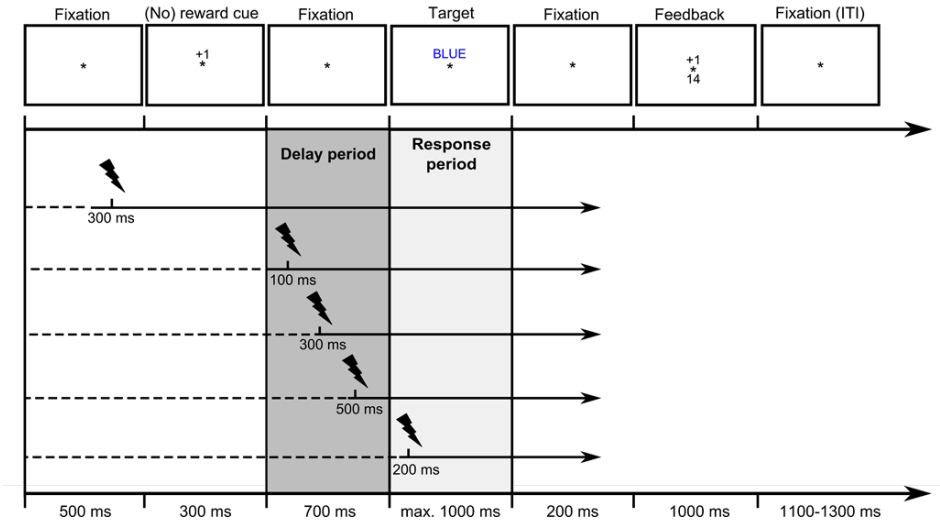

Fig. 1. Schematic illustration of the trial procedure. Each trial began with the presentation of a fixation asterisk (500 ms) and a baseline TMS pulse could be applied (300 ms) after fixation onset. Subsequently, a reward ("+1") or a non-reward ("+0") cue (300 ms) was presented. During the following cue-target delay period (700 ms) a TMS pulse could be applied (400, 600, or 800 ms after cue onset). Thereafter, the target was presented (max. 1000 ms) and the participant was required to provide a left or right index finger button press. Occasionally, a TMS pulse was applied 200 ms after target onset. After providing a correct response, a fixation period (200 ms) and feedback (1000 ms) followed. If individuals did not provide a correct or a timely response, the upper part of the feedback screen was replaced by a "fout" (Dutch for "wrong") or a "te laat" (Dutch for "too late") message, respectively. Trials were interspersed by a jittered inter-trial fixation interval (1100-1300 ms).

It has been shown that Stroop congruency effects could be compromised by word-ink color contingencies (Schmidt, 2013; Schmidt & Besner, 2008; Schmidt, Crump, Cheesman, & Besner, 2007). Specifically, in the canonical four colors Stroop task, the word (e.g., BLUE) could be displayed in one congruent (i.e., blue) and three incongruent (i.e., red, yellow, green) ink colors, resulting in the possibility that "participants implicitly learn contingencies (i.e., correlations) between words and responses and then use these contingencies to predict the specific response associated with each distracting word" (Schmidt & Besner, 2008, p. 515). To avoid data corruption by stimulus-response contingencies, Stroop stimuli were presented in two ink colors only (i.e., congruent and incongruent respectively). Thus, the words 'RED' and 'GREEN' were presented in red or green ink-color and the words 'YELLOW' and 'BLUE' were displayed in yellow or blue ink-color. Importantly, ink-colors that were associated with the same word stimulus were mapped onto different response buttons (e.g., the word 'RED' in red and green ink-color required a left and right key press, respectively), such that the task-irrelevant stimulus feature (i.e., the word semantics) was not predictive of the correct response key.

Participants had to complete 512 trials in total. Thereof, on 6.25% (32 trials) of all trials baseline CS excitability was examined ($TMS_{baseline}$), 56.25% (288 trials) included delay period TMS equally distributed across three time epochs ($TMS_{delay+400}$, $TMS_{delay+600}$, $TMS_{delay+800}$), 18.75% (96 trials) included a target TMS pulse

($TMS_{target+200}$), and another 18.75% (96 trials) of all trials did not include any TMS. Trials were separated into four experimental blocks that were separated by at least 30-s breaks. The experiment consisted of an equal amount of randomized trials that were balanced across responses (left/right FDI), congruency, and (non-)reward cues. Participants completed the experimental task within ~45 minutes.

Data analysis: behaviour

It has been shown that the application of TMS over motor areas can influence subsequent behavioral performance (Hasbroucq, Kaneko, Akamatsu, & Possamaï, 1997). To avoid corruption of behavioral data by TMS over M1, the behavioral analysis was based on trials that did not include any TMS pulse. These trials were controlled for premature (<100 ms) and omitted responses (>1000 ms). Additionally, only correct trials that were preceded by correct responses on the previous trial were included in the RT analysis. On average, using these criteria resulted in the exclusion of ~11.2% trials. Subsequently, RTs and the percentage correct trials were submitted to a repeated-measures ANOVA (rANOVA) with motivational cue (non-reward, reward) × congruency (congruent, incongruent) as within-subject factors.

Data analysis: CS excitability

Data preprocessing of CS changes was performed offline using MATLAB software (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States). For

each trial that included a TMS pulse, the peak-to-peak amplitude of the MEP was calculated. One second EMG epochs enclosing the interval 500 ms prior to until 500 ms after the actual event (i.e., TMS pulse) were extracted from the data. Within the time window of 20-40 ms succeeding the TMS pulse an automated algorithm identified the MEP amplitude. Trials were controlled for EMG background activity during the 500 ms epoch prior to the TMS pulse. If the root mean square of the background activity was on average larger than 0.1 mV during this 500 ms epoch, the trial was excluded from further analysis. Trials were also excluded when behavioral responses occurred within 100 ms after target onset or included response omissions (>1000 ms), as well as when an incorrect response was provided, when the current trial followed an incorrect response on the previous trial, and when the response took place at the same time as TMS application. Additionally, for each condition respectively (i.e., $TMS_{baseline}$, TMS_{delay}, and TMS_{target}), trials were excluded when the MEP amplitude was above or below three standard deviations from the condition mean MEP. Using these criteria resulted in the exclusion of 26.9% ($TMS_{baseline}$), 28.5% (TMS_{delay}), and 31.5% (TMS_{target}) trials.

CS changes were calculated relative to baseline CS excitability. First, the mean amplitude of TMSbaseline was calculated for each individual separately. Consequently, the mean CS excitability for each condition and participant was determined (i.e., $TMS_{delay+400}$, $TMS_{delay+600}$, $TMS_{delay+800}$, and $TMS_{target+200}$). Subsequently, CS

excitability was calculated relative to baseline expressing CS excitability changes in percentage scores: (Condition/Baseline-1)×100 (e.g., Lebon et al., 2015). Using this formula, values above or below zero are indicative of increased CS excitability and CS suppression, respectively.

In order to examine reward-related CS changes during task-preparation, a 2×3 rMANOVA with motivational cue (reward, non-reward) × stimulation epoch ($TMS_{delay+400}$, $TMS_{delay+600}$, $TMS_{delay+800}$) was performed on the electrophysiological data.

To inspect CS changes during action execution, data from TMStarget+200 were submitted to a 2×2 rMANOVA with motivational cue (reward, non-reward) and congruency (congruent, incongruent) as within-subjects factor. All statistical analyses were performed using SPSS statistical software (Version 22.0. Armonk, NY, USA: IBM Corp.).

RESULTS

Behavior: main analysis

RTs that followed a reward compared to a non-reward cue were overall faster (592ms vs. 619ms) ($F(1,37)= 25.810$, $p<0.001$, $\eta p^2=0.411$) and RTs were faster for congruent compared to incongruent targets (590 ms vs. 620 ms) ($F(1,37)=26.986$, $p<0.001$, $\eta p^2=0.422$). Furthermore, and inconsistent with previous reports, there was a trend towards a significant interaction between motivational cue and congruency ($F(1,37)=3.297$, $p=0.078$, $\eta p^2=0.082$), indicating a larger congruency effect for potentially rewarded (37 ms) compared to non-rewarded trials (24 ms), see Fig. 2A.

Likewise, error rates (Fig. 2B) indicated marginally higher accuracy on targets following a reward compared to a non-reward motivational cue (96.6% vs. 95.1%) ($F(1,37)=4.067$, $p=0.051$, $\eta p^2=0.099$). There was a main effect of congruency suggesting higher accuracy on congruent compared to incongruent targets (96.8% vs. 94.9%) ($F(1,37)=4.241$, $p=0.047$, $\eta p^2=0.103$). However, both within-subject factors (i.e. motivational cue and congruency) did not interact ($F < 1$).

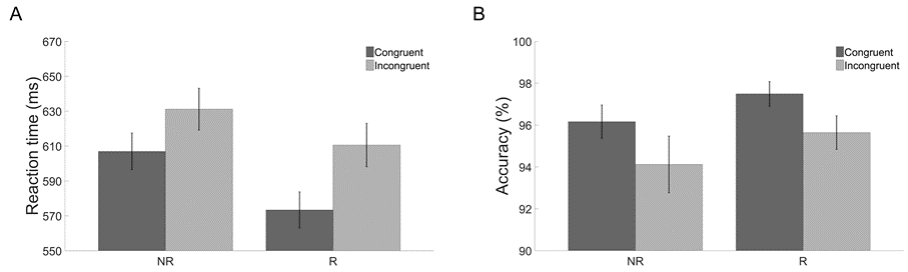

Fig. 2. Behavior. Mean reaction time (A) and accuracy (B) of no-TMS-pulse trials for (in-)congruent stimuli during (non-)reward anticipation. Bars depict one standard error of the mean.

Behavior: RT bin analysis

Because it has been shown that the Stroop effect increases over time (i.e., it is smallest for fast RTs and largest for slow RTs; Pratte et al., 2010), we reasoned that any motivational effect altering the size of the congruency effect should emerge specifically for trials with relatively slow RTs. Correspondingly, we ranked all trials based on RT, separately for reward/non-reward, for congruent/incongruent, and for each participant, and divided them into two bins (fast RTs, slow RTs).

The respective analyses revealed an obvious main effect of bin (Fig. 3; 522ms vs. 684ms) ($F(1,37)=1024.739$, $p<0.001$, $\eta p^2=0.965$). Importantly, results indicated a significant (three-way) bin by motivational cue and congruency interaction ($F(1,37)=5.263$, $p=0.028$, $\eta p^2=0.125$). Further analysis of this interaction showed that the motivational cue did not modulate the congruency effect for fast RTs

(F<1), however, for slow RTs, there was a significant interaction between motivational cue and congruency (F(1,37)=4.838, p=0.034, ηp^2=0.116). This was the result of the congruency effect being significantly larger for reward compared to non-reward anticipation (57 ms vs. 32 ms; t(37)=2.2, p=.034), and Fig. 3 suggests that this was especially due to changes in congruent RT.

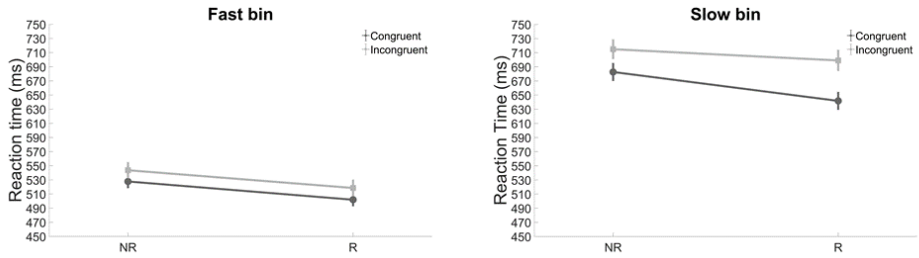

Fig. 3. Reaction time bins. Mean reaction time of no-TMS-pulse trials during non-reward (NR) and potentially reward (R) trials for congruent (dark grey) and incongruent (light grey) stimuli subdivided into fast (left panel) and slow (right panel) reaction time bins.

CS excitability: delay period

The analysis of the CS changes (Fig. 4) during the delay period revealed a main effect of stimulation moment (F(2,74)=8.137, p=0.001, ηp^2=0.180) indicating an decrease of CS excitability from the first to the last stimulation moment ($TMS_{delay+400}$=0.385%, $TMS_{delay+600}$=-1.187%, $TMS_{delay+800}$=-8.082%). Surprisingly, there was no significant

difference between motivational cues, (F(1,37)=1.280, p=0.265, ηp^2=0.033) suggesting that non-reward compared to reward anticipation (-1.845% vs. -4.078%, respectively) had statistically similar effects on CS excitability. No interaction between motivational cue and stimulation epoch was observed (F<1).

We also performed a slope analysis to compare CS suppression for reward and non-reward trials. Both reward and non-reward slopes deviated significantly from zero (t(37)=-2.690, p=0.011, and t(37)=-.2425, p=0.020, respectively) but were not significantly different from each other (t<1).

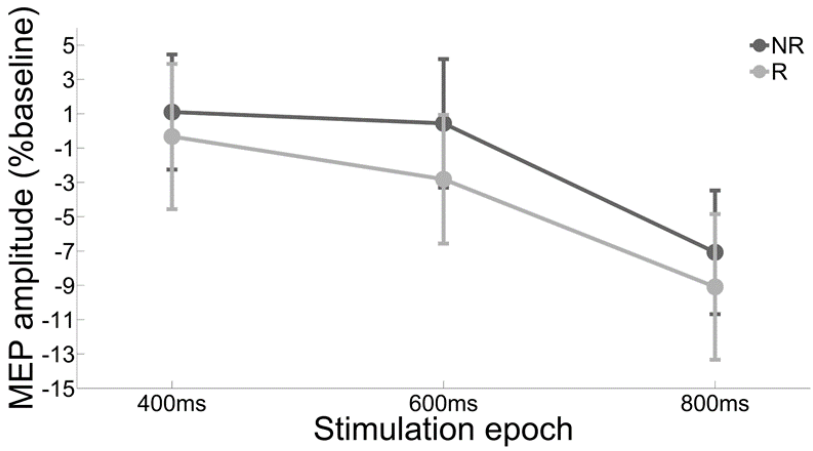

Fig 4. Delay period CS excitability. The graph depicts mean baseline-corrected MEP amplitudes during non-reward (NR) and reward (R) anticipation throughout the cue-target delay period for each stimulation epoch (400, 600, 800 ms after cue onset). Error bars depict one standard error of the mean.

In order to compare the current findings with the results from previous study, we omitted the baseline TMS pulse to analyze delay period CS changes using a Z-transformation (Bundt et al., 2016; Burle et al., 2002). These analyses confirmed our findings. Results, revealed no main effect of motivational cue ($F(1,37)=2.055$, $p=0.160$, $\eta p^2=.053$), and again indicated a main effect of stimulation epoch ($F(1,37)=6.179$, $p=0.003$, $\eta p^2=0.143$), but no interaction between motivational cue and stimulation epoch was observed ($F<1$).

CS excitability: target

The analysis of CS excitability changes during target presentation revealed no significant main effect for the anticipation of a motivational cue (NR=-4.19% vs. R=-9.06%; $F<1$), and neither for congruency (Congruent=-7.01% vs. Incongruent=-6.24%; $F<1$). Furthermore, there was no interaction observed between both of these factors ($F<1$).

Delay period CS excitability-behavior correlations

As evidence pertaining the link between preparatory CS suppression and behavioral measures is (if at all) scarce, we wanted to exploreif and to what extent changes in CS excitability during the delay period were associated with behavioral measures.

First, we examined whether the degree to which reward decreased RTs was associated with the CS excitability difference

between slopes during reward and non-reward anticipation. The RT reward effect during non-stimulation trials was calculated by subtracting the averaged RTs during reward anticipation trials from the averaged RTs during non-reward anticipation (i.e., positive difference scores indicate larger reward effects). For the CS effect, the difference score between non-reward and reward anticipation slopes was calculated (i.e., reward slope – non-reward slope; a positive difference score indicates stronger CS suppression for non-reward than for reward anticipation trials). This correlation was non-significant (r=-.087, p=.605). Also when we used the average difference between reward and non-reward excitiblity (instead of slope), the correlation is not significant (r=.040, r=0.813).

Second, we examined whether the size of the behavioral (i.e., RT) Stroop effect during non-stimulation trials was associated with the degree of CS suppression during the cue-target delay period. To that end, a behavioral index was calculated by subtracting the size of the Stroop effect (i.e., incongruent – congruent) of reward trials from the size of the Stroop effect of non-reward trials (i.e., a positive difference score reflects a larger Stroop effect for non-reward than for reward trials).This measure was then correlated with the above-mentioned difference of CS excitability slopes, but did not reach significance (r=.270, p=.101).

DISCUSSION

Action preparation is associated with CS suppression and recent studies have shown that changes of motivational states are associated with the modulation of preparatory CS excitability (Bundt et al., 2016; Chiu et al., 2014; Gupta & Aron, 2011; Suzuki et al., 2014; Vassena et al., 2015). In the present study, we sought to replicate previous findings (Bundt et al., 2016) showing that during the cue-target delay period reward compared to non-reward anticipation results in initially larger CS excitability after cue presentation and is then followed by a linear decrease, resulting in relatively stronger CS suppression just before target onset. The present findings revealed that reward may modulate behavioral measures and indices (e.g., congruency effect), in contrast to previous findings, however, CS suppression was generally not significantly modulated by reward.

Behaviorally, we observe two interesting effects. First, RTs decreased for reward cued trials, and second, the Stroop effect became larger for reward cued trials. This was mainly due to the finding that during reward compared to non-reward anticipation, individuals seemed to respond much faster to congruent stimuli, while the difference (between reward and non-reward) was much less for incongruent stimuli. This pattern was particularly true for slow reaction times, which is in line with results showing that the Stroop congruency effect increases over time (i.e., it is smallest for fast RTs and largest for slow RTs; Pratte, Rouder, Morey, & Feng,

2010).However, the finding that reward compared to non-reward anticipation helped to speed up reaction times specifically during congruent stimuli and did not affect incongruent stimuli as much may (partially) be in contrast to previous research that argues that heightened motivation enhances attentional filtering. For example, Padmala and Pessoa (2011) let individuals perform a (Stroop like) compound scene-plus-word task in which pictures of houses and buildings were overlaid by corresponding words (HOUSE, BLDNG) or with a neutral letter string (XXXXX), thereby creating (in-)congruent or neutral picture-word pairs. Participants were asked to respond to the images by providing a button press. Crucially, previous to target presentation, a reward cue was presented ($20 or $00) indicating whether or not participants could receive reward for fast and accurate responses, respectively. Padmala and Pessoa (2011) found that reward decreased the interference (incongruent vs. neutral) as well as the facilitation effect (congruent vs. neutral) and interpreted it as being coherent with the notion that motivation enhances attentional filtering reducing the impact of the task-irrelevant stimulus (i.e., word). Another study found a diminished Stroop effect in high-reward compared to low-reward blocks (Soutschek et al., 2014), while others reported a reduction of the Stroop effect for error rates but not for reaction times (Veling & Aarts, 2010) or did not find any motivational reduction of Stroop interference (van den Berg et al., 2014). Thus, evidence regarding a change of the Stroop effect by reward is still not always unequivocal

and the current findings add to this ambiguity. In contrast to the finding that reward diminishes the Stroop effect (Padmala & Pessoa, 2011; Soutschek et al., 2014; Veling & Aarts, 2010), our data showed the opposite pattern, namely, the Stroop (interference) effect was increased on potentially rewarded compared to non-rewarded trials. Individuals showed particularly faster RTs for congruent compared to incongruent during reward anticipation, which may suggest that in the current task reward increased the facilitation effect. As the current study did not include neutral stimulus features, future research needs to incorporate these stimulus features to unambiguously distinguish between facilitation and interference effects in the Stroop task.

In terms of CS excitiblity, the results show a gradual increase of suppression towards the moment of target presentation. In our previous study (Bundt et al., 2016) the experimental design did not allow to determine whether non-reward anticipation was associated with CS suppression during the delay period due to a lack of a baseline TMS pulse. In the present study, however, we implemented such a baseline pulse and observed that irrespective of the reward manipulation there was a transient increase of CS suppression relative to baseline throughout the delay period that had its peak just before target onset (for a discussion of the informativeness of baseline TMS pulses, see Bestmann & Krakauer, 2015; Labruna, Fernandez-del-Olmo, & Ivry, 2011). In line with previous findings (Duque & Ivry, 2009; Greenhouse et al., 2015; Lebon et al., 2015), these results

generally suggest that action preparation is associated with CS changes. Moreover, they corroborate the notion that although the relevant response is unknown across the delay period, the preparation of (multiple potential) actions is associated with CS suppression. This, in turn, may be in line with the assumption that preparatory CS suppression reflects an impulse control mechanism that safeguards against premature response execution (Duque, Labruna, Verset, Olivier, & Ivry, 2012; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010). However, CS suppression could also reflect a gain modulation, thereby increasing the signal-to-noise ratio (SNR) within the motor system (Greenhouse et al., 2015). Within the motor system, an increased SNR would result in an improved sensitivity to excitatory inputs and may be implemented by preparatory inhibition (for a discussion of functional accounts of preparatory inhibition, see Duque, Greenhouse, Labruna, & Ivry, 2017). In the present study, results did not reveal a modulation of CS excitability by reward during target presentation (i.e., 200 ms after target onset). Although based on a previous study (Bundt et al., 2016), the chosen TMS pulse timing of 200 ms was most likely too early to detect any target-related differences in CS excitability. It has been shown, for example, that semantic conflict in the Stroop task occurs approximately 300-450 ms post-stimulus (Zurrón, Pouso, Lindín, Galdo, & Díaz, 2009). Thus, it may be worthwhile to examine conflict in the Stroop task and its impact on CS excitability during later post-stimulus time epochs (i.e., >=300 ms).

Overall, the results of this study revealed that reward improves behavior, but fails to modulate preparatory CS excitability. The discrepancy between the current results and previous findings pertaining CS excitability may be attributable to differences between tasks such as task difficulty. To that effect, in the current task, increased task difficulty may have induced overall increased preparatory CS suppression irrespective of motivational cuing.

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CHAPTER 5

REWARD ANTICIPATION CHANGES CORTICOSPINAL EXCITABILITY DURING TASK PREPARATION DEPENDING ON RESPONSE REQUIREMENTS AND TIME PRESSURE

The preparation of an action is accompanied by transient corticospinal (CS) suppression, and recent evidence has shown that motivation modulates this process. Specifically, when a cue indicated that a reward could be obtained, CS excitability initially increased, followed by a more pronounced CS suppression. In two experiments, we used variants of the Go/NoGo task to examine whether this early increase of CS excitability was intrinsic to the anticipation of reward or due to the preparation of an actual response that may be associated with an increased allocation of effort for potentially rewarded trials. In two experiments that modulated time pressure in Go-trials through different time-out procedures, we used single-pulse transcranial magnetic stimulation (spTMS) over the left primary motor cortex (M1) early (shortly after cue-onset) or late (shortly before target onset) preceding target onset to examine CS excitability during motivated (non-)action preparation. Electromyography

(EMG) was obtained from the right first dorsal interosseous (FDI) muscle. Both experiments revealed stronger CS suppression for Go compared to NoGo trials throughout the delay period, suggesting CS suppression to be strongly modulated by the preparation of an actual action. Most interestingly, only the imposition of a strict time-out procedure in Exp. 2 resulted in CS excitability being largest during reward anticipation for Go responses for the early stimulation epoch and then sharply decreased, while CS excitability remained unchanged during non-reward anticipation. Our findings suggest that reward effect on CS excitability is dependent on the preparation of an actual action, as well as on temporal requirements (e.g., time pressure) invoked by the task.

INTRODUCTION

The advance preparation of a task and its associated actions enables humans to anticipate future environmental demands in a flexible manner (Bode & Haynes, 2009; Brass & Von Cramon, 2002, 2004). Changes in corticospinal (CS) excitability have been observed during action preparation using transcranial magnetic stimulation (TMS) with concurrent electromyography (EMG) (Duque & Ivry, 2009; Greenhouse, Sias, Labruna, & Ivry, 2015; Lebon et al., 2015). To assess action preparation, typically, a cue-target delay paradigm is employed in which an (un)informative preparatory cue specifies which effector is to be engaged after a short delay period at the onset of an imperative signal (Duque & Ivry, 2009). During the cue-target delay period, TMS is applied over the primary motor cortex (M1) to examine CS state changes in the motor system during the anticipation of an action. It has been shown that after an informative cue, CS excitability is usually suppressed within the cue-target delay period for the task-relevant effector (i.e., the effector executing the cued response) relative to a baseline measure (Duque & Ivry, 2009) as well as for the task-irrelevant muscle (Greenhouse et al., 2015). Additionally, CS suppression was also observed after uninformative cues during the delay period for potentially task-relevant muscles (Bundt, Abrahamse, Braem, Brass, & Notebaert, 2016; Duque & Ivry, 2009). Although the extent of such suppression may be limited to motor representations that are functionally or anatomically related

(Duque, Greenhouse, Labruna, & Ivry, 2017), these findings suggest that CS suppression may represent a relatively broad mechanism reflecting the concurrent preparation of multiple potential actions through mutual inhibition between neural populations representing action parameters (Cisek, 2006, 2007). It has been proposed that each action representation competes with each other in a parallel and continuous fashion. This "tug-of-war" between distinct action representations is assumed to be modulated by upstream processes (Duque & Bestmann, 2016), such as by the estimation of biomechanical costs (Cos, Duque, & Cisek, 2014) and the subjective value of responses (Klein-Flügge & Bestmann, 2012), biasing the selection of one action alternative over the other.

In line with these findings and most relevant for the current study, reward was found to dynamically modulate CS excitability during action preparation as well (Chiu, Cools, & Aron, 2014; Freeman & Aron, 2016; Gupta & Aron, 2011; Kapogiannis, Campion, Grafman, & Wassermann, 2008; Klein, Olivier, & Duque, 2012; Suzuki et al., 2014; Thabit et al., 2011; Vassena, Cobbaert, Andres, Fias, & Verguts, 2015). Collectively, these studies suggested that increased motivation is accompanied by increased CS excitability during the delay period (e.g., the preparation of a reward-predictive response compared to a non-reward predicting response leads to higher CS excitability). However, we recently showed that CS excitability decreased throughout the delay period after an effector-uninformative but reward-promising cue, whereas CS excitability

did not change significantly for neutral cues (Bundt et al., 2016). The decrease of CS excitability was due to a large positive CS excitability difference between reward compared to non-reward cues for early (i.e., reward > non-reward) compared to late (i.e., reward < non-reward) stages during the delay period, which suggested a relatively fast effect of increased motivation (i.e., reward) on motor system state changes. Given these findings, the current study aimed to examine whether the initial increase in CS excitability during reward compared to non-reward anticipation was a general or a task-specific effect on the motor system. We reasoned that if the mere perception of reward induces a general effect within the motor system and thereby leads to changes in CS excitability, it should occur irrespective of whether or not an action must be prepared. In contrast, if the observed effect was due to specific-task and response requirements, reward compared to non-reward anticipation should not result in increased CS excitability when the task is unassociated with the preparation of any response. A secondary goal of the current study was to explore the temporal development of CS excitability changes during cued action versus non-action preparation. To our knowledge, this has not been investigated so far but is fundamental to whether preparatory CS suppression is contingent upon action preparation. To that end, we designed a task in which a Go/NoGo cue indicated whether (or not) a subsequent response must be prepared. After a short delay, a motivational cue was presented informing individuals whether or not they could accumulate an extra point for

(potentially fast and) accurate performance. A second delay period followed and the target (i.e., circle) left or right from fixation was shown upon which individuals were required to either withhold or execute a response. Single-pulse TMS (spTMS) was applied over the left M1 and EMG was obtained from the right first dorsal interosseous (FDI). We assessed CS excitability during three stimulation epochs: a) within the inter-trial-interval (ITI) 200 ms before the onset of the action cue to examine baseline CS excitability, b) 400 ms and c) 800 ms after the motivational cue onset to examine CS excitability during early and late stages of action preparation. Behaviorally, we predicted that on Go trials, reward compared to neutral cues help to speed up responses. Neurophysiologically, we hypothesized that if reward induces an automatic effect on the motor system, we would observe higher CS excitability for reward compared to neutral cues for both Go and NoGo during the early (i.e., 400 ms after motivational cue onset) stimulation epoch. However, if the motivational effect on the motor system is contingent upon the preparation of an actual response, we expected to find a task-dependent (i.e., Go vs. NoGo) modulation of CS excitability for reward compared to neutral cues during the early stimulation epoch.

Both of our hypotheses were examined in two experiments. In Exp. 1, we employed a liberal response deadline that was based on the mean reaction times during a preceding practice block, allowing participants to respond without much time pressure. In Exp. 1, however, there was no significant modulation of CS excitability by

motivation, which is inconsistent with our previous findings (Bundt et al., 2016). We reasoned that when response thresholds were too liberal, the chance to receive reward might lose its motivational effect, as it is too self-evident to obtain the reward even if one is not performing optimally. Therefore, in Exp. 2, we employed a stricter response threshold that took trial-by-trial variations into account (Elchlepp & Verbruggen, 2017; Leiva, Parmentier, Elchlepp, & Verbruggen, 2015). Our rationale was that setting a stricter response threshold may result in the tendency to perform more optimally (i.e., motivation to perform well is increased) as the probability of receiving a reward strongly decreases if one is performing sub-optimally.

EXPERIMENT 1

In this experiment we examined the influence of reward on CS excitability during the preparation of (no) action under no (or only little) time pressure. We hypothesized that if the effect of motivation on CS excitability was dependent on the preparation of a response, reward would only affect CS excitability during Go trials. However, if motivation had a non-specific effect on CS excitability, reward should modulate CS excitability during NoGo and Go responses equally.

METHODS

Participants

Twenty-five participants took part in the first experiment. One subject was excluded, however, because (s)he was not able to follow the task instructions such that the statistical analyses reported below were based on the data of the remaining twenty-four individuals (17 female; 22.13 ± 2.23 years of age). Participants were screened for psychiatric and neurological disorders, as well as for factors that could intervene with a safe application of TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). All participants gave written informed consent and were monetarily compensated (25€) for their participation in the study. Moreover, participants were informed that the best-performing individual would receive an extra bonus in the

form of a 25€ voucher for a local multimedia store. The study was in agreement with the Declaration of Helsinki and was approved by the local ethical committee at Ghent University Hospital.

Stimuli and procedure

Participants were seated in a comfortable chair in front of a computer screen with an eye-to-screen distance of approximately 50 cm. Responses were provided via a QWERTY keyboard that was turned 180°, i.e. with the function keys facing the participant (c.f., Bundt et al., 2016; Klein et al., 2012; Klein, Petitjean, Olivier, & Duque, 2014). Participants were required to place their left and right index finger tips on the keyboard between the F8 and F9, and F4 and F5 buttons, respectively. A response was executed by performing an index finger abduction movement towards the medial response key (i.e., either an abduction movement with the left index finger towards the F8 key, or an abduction movement with the right index finger towards the F5 key) and to eventually press this button.

Each trial started with an asterisk presented in the center of the screen for 500 ms (see Fig. 1 for a schematic illustration of the trial procedure). On a proportion of trials, baseline CS excitability was assessed during this fixation period (see below). Subsequently, either a ")(" or "X" was presented for 300 ms above fixation (i.e., action cue). These symbols indicated whether or not an action (i.e., Go vs. NoGo) was required at target onset, respectively. This was followed by a 600 ms fixation period after which the motivational cue was shown for

300 ms above fixation. Specifically, "+1" and "+0" indicated that reward or no reward could be obtained for fast and accurate performance on current trial, respectively. Note that participants received reward on NoGo trials as well, but only if they managed to omit a manual response. To ensure that participants attended the reward information even after they were informed that they did not need to respond (i.e., during NoGo trials), the motivational cue was occasionally presented in blue ink color (i.e., catch trial). On these trials, participants were asked to provide a verbal response (i.e., they were required to say "blue") as soon as they detected a blue-colored reward cue (c.f., Gupta & Aron, 2011). Prior to the experiment, participants were told that if they fail to detect a sufficient amount of blue-colored motivational cues, their accumulated reward would be withheld (Gupta & Aron, 2011). After the presentation of the (potentially colored) motivational cue, another fixation period of 600 ms (i.e., delay period) followed in which CS excitability was examined on a proportion of trials (see below). If the motivational cue was presented in blue ink color, the trial was terminated after this delay period and a new trial was initiated. If the motivational cue did not indicate a catch-trial, however, the action-cue reappeared above fixation and was accompanied by a circle presented left or right from it (i.e., target stimulus). Participants were required to provide a left or right index finger response when the target appeared left or right of fixation, respectively. The duration of the presentation of the target (and simultaneously the duration of the response deadline) was

determined by the mean reaction time during a preceding practice phase (see below). After individuals provided a correct and timely response, a fixation period followed (200 ms) and subsequent feedback was provided (1000 ms) indicating whether or not reward has been obtained on current trial (i.e., "+1" or "+0" appeared above fixation) and how much reward has been accumulated throughout the course of the experiment (i.e., as a number appearing below fixation). When the participant provided a wrong or a late response, "fout" (Dutch for "wrong") or "te laat" (Dutch for "too late") was presented above fixation instead. Each trial was separated by a jittered inter-trial-interval (ITI) fixation period (900-1100 ms).

On a proportion of trials, TMS was applied over the left M1 during three different stimulation epochs. TMS pulses were applied during the ITI fixation period 200 ms prior to the presentation of the action cue to examine CS baseline excitability ($TMS_{baseline}$). To examine CS excitability throughout early and late stages of the delay period succeeding the presentation of the motivational cue (i.e., during the motivational cue-target delay period), TMS pulses were applied either 100 ms (TMS_{early}) or 500 ms after the motivational cue offset (TMS_{late}).

In total, the experiment consisted of 612 trials composed into five blocks. The first block (68 trials; thereof four catch-trials) served as practice phase where individuals were able to familiarize themselves with the experimental task. The mean reaction time of participants on correct Go trials during this practice phase was

eventually used as target response deadline during the subsequent experimental blocks. No TMS was applied during the practice phase and trials were balanced across action cues (Go/NoGo), motivational cues (NR/R), and responses (right/left).

The practice phase was followed by four experimental blocks (136 trials each; test phase) which did include TMS application. In total, the test phase comprised 32 trials including $TMS_{baseline}$, 160 trials TMS_{early}, 160 trials TMS_{late}, and 160 trials not including any TMS as well as 32 catch-trials (i.e., blue cue trials). Each block consisted of randomized trials that were balanced across action cues (Go/NoGo), motivational cues (NR/R), TMS epoch (early/late) and responses (right/left).

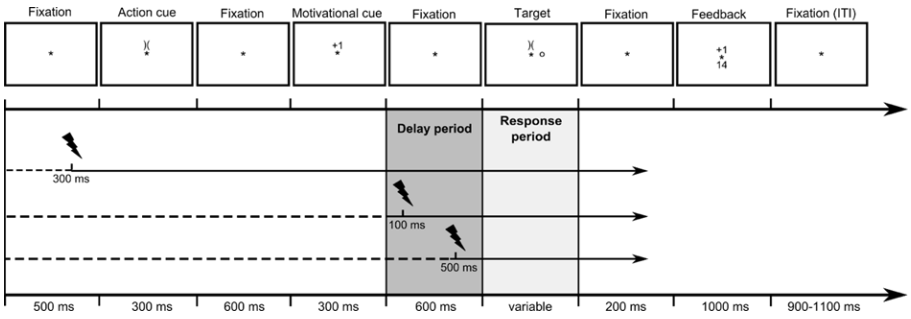

Fig. 1. Schematic trial procedure. Each trial started off with an fixation asterisk presented in the center of the computer monitor for 500 ms. Thereafter, an action cue (here a Go cue) was presented for 300 ms above fixation, which indicated whether or not (")(" or "X") participants needed to prepare a response on the current trial. After another fixation period (600 ms) the motivational cue ("+0" or "+1")

was presented above fixation (300 ms). After the following cue-target delay period (600 ms), the target (i.e., circle) was presented left or right from fixation alongside with the action cue above fixation. The response deadline was variable such that it depended on the mean reaction time during a first practice block in Exp. 1, and was determined by the 3-down/1-up algorithm in Exp. 2. If individuals responded to the target within the deadline during Go or omitted a response during NoGo trials, a short fixation period followed (200 ms) and was then replaced by visual feedback, showing whether or not a reward was obtained and how much reward has been accumulated. Each trial was completed by a fixation period jittered in duration between 900 and 1100 ms. TMS was applied at three different timings. A baseline TMS pulse was applied 200 ms before the onset of the action cue. TMS was applied early or late (400 ms or 800 ms after the onset of the motivational cue) during the cue-target delay period to examine the effect of motivation on CS excitability. Occasionally, blue-colored motivational cues (i.e., catch-trials) were interspersed to ensure that participants attend to the motivational cue even when no response must be prepared (i.e., during NoGo trials). Individuals were required to identify such catch trials by naming the color of the cue every time it appeared in blue ink-color. After the presentation of a catch-stimulus, a fixation period of 600 ms followed and the trial was aborted.

TMS stimulation and EMG recordings

TMS stimulation and EMG recording procedures were identical to our previous study (Bundt et al., 2016). spTMS was applied over left M1 and EMG was obtained from the right first dorsal interosseous (FDI). The resting motor threshold (rMT) of all individuals was M=60.75% ± SD=6.6% of the maximal stimulator output and the eventual TMS pulse intensity was set to 110% of the rMT.

Data analysis: behaviour

The stimulation of the motor system temporally close to a response has been shown to influence behavioral performance (Hasbroucq, Kaneko, Akamatsu, & Possamaï, 1997). To exclude the possibility that the magnetic stimulation of M1 could interfere with behavioral measures, the behavioral analysis of both experiments was based on trials that did not include any TMS pulse. Furthermore, only correct trials were included in the analysis that followed a correct response on the previous trial, and that did not include response omissions (i.e., RT < individual mean RT in practice block) or premature responses (RT > 100ms). Furthermore, trials that followed a catch-trial were excluded as well. For Go trials, RT and the percentage of response omissions were then submitted to a paired-samples t-test (NR vs. R), respectively. For Go and NoGo trials, percentage correct (Go/NoGo) responses were submitted to a paired-samples *t*-test (NR vs. R), respectively.

Data analysis: CS excitability

CS excitability changes were analyzed offline using MATLAB software (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States). One-second EMG epochs surrounding the TMS pulse (-500 ms to 500 ms relative to the TMS pulse) were extracted. An automated search-algorithm identified the peak-to-peak motor-evoked-potential (MEP) amplitude during a window of 20-40 ms succeeding the TMS pulse. Prior to the experiment, it was defined to discard MEPs that were affected by pre-contraction (RMS of background activity exceeding 0.1 mV during the 500 ms prior to the TMS pulse) or that were identified as outliers (above or below three standard deviations from the mean calculated for baseline and delay-period TMS separately). Valid trials were submitted to a repeated-measures ANOVA (rANOVA) with action cue (Go, NoGo) × motivational cue (no reward, reward) × stimulation epoch (early, late) as within-subjects factors.

RESULTS

Behavior

Go trials RTs were significantly faster during reward compared to non-reward anticipation (Fig. 2; 410 ms vs. 427 ms; $t(23)$=-4.629, p<0.001). Percentage correct responses on Go trials were not significantly different for potentially rewarded and non-rewarded trials (99.6% vs. 99.5%; t<1). On NoGo trials, percentage correct responses were not significantly different during reward (99.6%) compared to non-reward (100%) anticipation ($t(23)$=1.812, p=0.083). On Go trials, response omissions during reward compared to non-reward anticipation were statistically not different (1.14% vs. 1.10%; t<1).

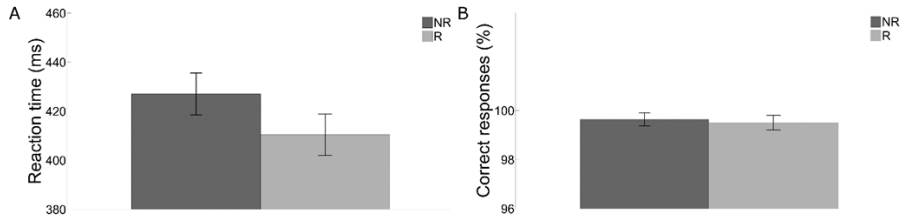

Fig. 2 Mean reaction time (A) and percentage correct responses (B) for non-reward (NR) and reward (R) anticipation in Exp. 1.

CS excitability

Fig. 3 illustrates the CS excitability changes for Exp. 1. There was no main effect of action cue (F<1), nor a main effect of motivational cue ($F(1,23)$=1.301, p=0.266, ηp^2=0.054). However, there

was a main effect of stimulation epoch ($F(1,23)=13.658$, $p=0.001$, $\eta p^2=0.373$) indicating that CS excitability was significantly larger during early compared to late stimulation epochs (0.05% vs. -9.87%). There was also a significant interaction between action cue and stimulation epoch ($F(1,23)=6.503$, $p=0.018$, $\eta p^2=0.220$). This two-way interaction was due to a significant difference of CS excitability between early compared to late stimulation epochs for Go trials (2.81% vs. -13.35%; $F(1,23)=14.334$, $p<0.001$, $\eta p^2=0.384$), but not for NoGo trials (-1.78% vs. -6.38%; $F(1,23)=2.702$, $p=0.114$, $\eta p^2=0.105$), indicating preparatory CS suppression only when an actual action needs to be prepared. No other two-way (ps>0.225) or three-way ($p=0.162$) interaction effects were observed.

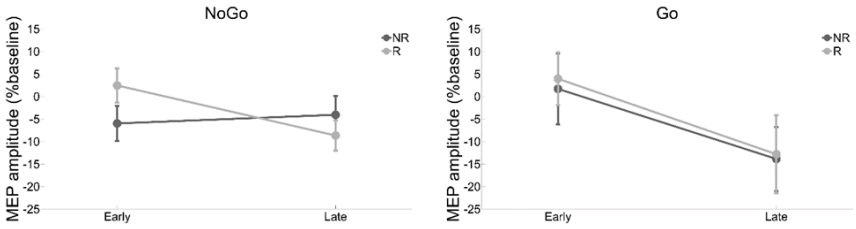

Fig. 3 CS excitability changes for Exp. 1. The figure shows the averaged CS excitability changes relative to baseline for NoGo (left panel) and Go (right panel) responses during non-reward (NR) and reward (R) anticipation for both (early and late) stimulation epochs.

CS excitability – behaviour correlations

We were interested to what extent CS excitability changes throughout the delay period were associated with behavioral changes. To examine the motivational effect on CS excitability across the delay period, we calculated the difference score between the CS excitability (i.e., between early and late stimulation epochs) during non-reward and reward trials (non-reward difference – reward difference; a positive difference score indicates a larger CS excitability difference during reward anticipation). The reward effect on RTs was calculated by subtracting the mean RT during potentially rewarded trials from the mean RT of non-reward trials. The RT reward effect was calculated for Go trials and trials that did not include TMS stimulation, only (a positive difference score indicates faster RTs for reward compared to non-reward anticipation trials). However, the correlation between these two variables was not significant (r=-.152, p=.478).

Yet, when calculating the average CS excitability difference (i.e., irrespective of stimulation epoch) between (non-)reward anticipation there was a positive correlation with the behavioral RT reward effect (r=.429, p=.037), suggesting that a stronger reward effect on CS excitability (i.e., relatively stronger CS suppression during reward compared to non-reward anticipation) was associated with a larger behavioral reward effect.

Discussion

The first experiment examined the influence of reward on CS excitability during the preparation of (no) action under no (or only little) time pressure. Specifically, a short initial practice phase determined the time participants had to respond to the target (i.e., response deadline) throughout the rest of the experiment. Given the low amount of response omissions (R=1.14% vs. NR=1.10%), the chosen response deadline turned out to be very liberal, potentially obscuring the results of the present experiment. Behaviorally, the prospect of receiving reward resulted in behavioral improvements. In contrast to our initial hypothesis, however, no effect of reward on CS excitability was obtained.

EXPERIMENT 2

Given the literature background, the fact that the findings on CS excitability in Exp. 1 contrasted with our initial hypothesis raised questions about our exact implementation of the task, and we reasoned that the task may not have been sufficiently engaging for participants to actually discriminate between non-reward and reward cues. With liberal response deadlines (Exp. 1) reward may have lost its motivational effect to some extent as it is too self-evident to obtain the reward even if one is not performing optimally (e.g., by providing relatively slow responses). In order to emphasize the instrumentality of fast responding, we employed a stricter response deadline in Exp. 2, which encouraged faster responding and therefore tighter control over task preparatory processes (Elchlepp & Verbruggen, 2017; Leiva et al., 2015).

METHODS

Twenty-three individuals participated (13 female; 21.4 ± 1.8 years of age). Stimuli and trial procedure, TMS and EMG parameters, as well as data analyses were identical to Exp. 1 except for the following changes. First, the duration of the target presentation (and therefore the target response deadline) was determined by an adaptive tracking procedure (3-down/1-up) that allowed for the continuous adjustment of the response deadline. Specifically (and irrespective of the reward

condition), the adaptive tracking procedure subtracted 25 ms from the response deadline when the participant was able to provide three correct succeeding Go responses in time, and added 25 ms to the response deadline when the participant made an erroneous or late response (c.f., Elchlepp & Verbruggen, 2017; Leiva et al., 2015).

Furthermore, the duration of the experiment was slightly adjusted by decreasing the number of trials of some conditions. In total, the initial practice block consisted of 68 trials equal to Exp. 1. Thereafter the four experimental blocks (112 trials each, test phase) were comprised of 32 trials of TMSbaseline and catch-trials, respectively. Moreover, 128 trials of TMS_{early}, TMS_{late}, and non-stimulation trials were included, respectively. Equivalent to Exp. 1, each block consisted of randomized trials that were balanced across action cues (Go/NoGo), motivational cues (NR/R), TMS epoch (early/late) and responses (right/left).

The rMT was M=60.3% ± SD=7.3% of the maximal stimulator output (note that the rMT data was missing for one subject, such that the rMT mean and SD reported here are based on all other individuals).

RESULTS

Behavior

Go responses were significantly faster for reward compared to no-reward trials (366 ms vs. 381 ms; $t(22)=3.279$, $p=0.003$) (Fig. 4). The percentage of correct responses on Go trials was not significantly different for non-reward (98.91%) compared to reward (99.46%) anticipation ($t(23)=-1.279$, $p=0.214$). Neither were percentage correct responses during reward (99.56%) compared to non-reward (99.56%) anticipation different on NoGo trials ($t<1$). On Go trials, significantly more response omissions (i.e., responses that were not provided within the response deadline) occurred during non-reward (25.4%) compared to reward (15.6%) anticipation trials ($t(22)=-3.934$, $p=0.001$).

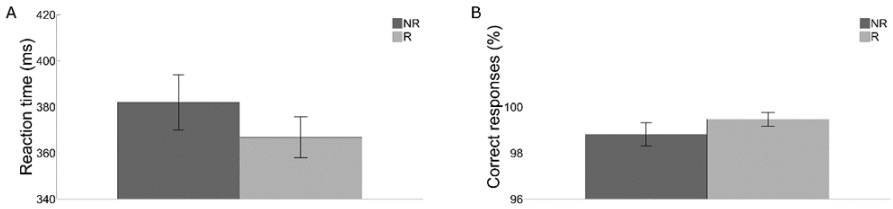

Fig. 4. Mean reaction time (A) and percentage correct responses (B) for non-reward (NR) and reward (R) anticipation in Exp. 2.

CS excitability

Fig. 5 depicts CS excitability changes for Exp. 2. Results showed no significant main effect for task (NoGo=-6.7% vs. Go=5.8%;

$F(1,22)=1.650$, $p=0.212$) and neither an effect for reward (non-reward=-2.0% vs. reward=1.1%; $F<1$). However, CS excitability was significantly larger during early compared to late stages within the delay period (TMS_{early}=3.7% vs. TMS_{late}=-4.7%; $F(1,22)=7.130$, $p=0.014$, $\eta p^2=0.245$). Moreover, a significant interaction between action cue and stimulation epoch was obtained ($F(1,22)=5.254$, $p=0.032$, $\eta p^2=0.193$). This was the result of significantly larger CS excitability for Go responses during the early compared to the late stimulation epoch (13.99% vs. -2.43%; $F(1,22)=8.931$, $p=0.007$, $\eta p^2=0.289$), whereas CS excitability did statistically not change for NoGo trials between both stimulation epochs (-6.53% vs. -6.87%; $F<1$). Most interestingly, results indicated a significant three-way interaction between action cue, motivational cue and stimulation epoch ($F(1,22)=7.417$, $p=0.012$, $\eta p^2=0.252$). Further analysis of this three-way interaction revealed that while there was no significant main or interaction effect for NoGo trials (Fs <1), on Go trials, CS excitability across both stimulation epochs was significantly altered by motivation ($F(1,22)=6.594$, $p=0.018$, $\eta p^2=0.231$). This was due to significantly larger CS excitability during the early compared to the late stimulation epoch for potentially rewarded trials (23.36% vs. -5.62%; $F(1,22)=11.161$, $p=0.003$, $\eta p^2=0.337$), but not for non-reward trials (4.62% vs. 0.75%; $F<1$). Furthermore, we observed significantly larger CS excitability for potentially rewarded compared to non-rewarded trials during the early stimulation epoch (23.36% vs. 4.62%;F(1,22)=4.805, p=0.039,

ηp2=0.179), but not the late epoch, (-5.61% vs. 0.75%; $F(1,22)=1.469$, $p=0.238$, $\eta p^2=0.063$.

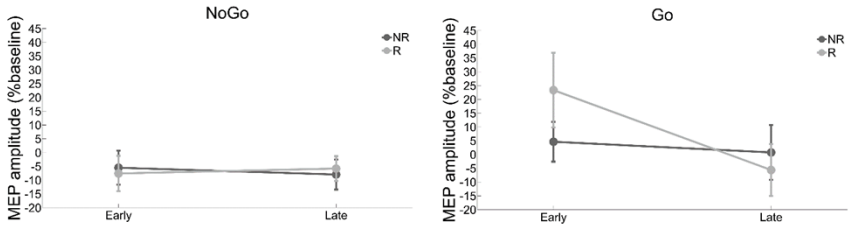

Fig. 5 CS excitability changes for Exp. 2. The figure shows the averaged CS excitability changes relative to baseline for NoGo (left panel) and Go (right panel) responses during non-reward (NR) and reward (R) anticipation for both (early and late) stimulation epochs.

CS excitability – behaviour correlations

Equal to the correlations reported above, we wanted to examine in Exp. 2 to what extent CS excitability changes throughout the delay period were associated with behavioral changes. We correlated the slope difference between non-reward and reward anticipation trials with the behavioral RT reward effect (same as above). This correlation did not reach significance ($r=-.045$, $p=.838$). Furthermore, we also calculated the absolute CS excitability difference between non-reward and reward anticipation trials and correlated the resultant difference with the behavioral RT reward effect. Again, no significant correlation was found ($r=.156$, $p=.476$).

Statistical comparisons between experiments

We were interested to explore whether a liberal compared to a strict response deadline modulated behavior and CS excitability differently. To that end, we merged the data from both experiments and submitted it to the above-mentioned rANOVA with Experiment as between-subjects factor.

In terms of behavior, imposing an adaptive compared to a liberal response deadline let to faster reaction times (374 ms vs. 418 ms; $F(1,45)=11.394$, $p=0.002$, $\eta p^2=0.202$), but did not result in accuracy differences (Exp. 1=99.58% vs. Exp. 2=99.14% accuracy; $F(1,45)=1.149$, $p=0.289$, $\eta p^2=0.025$). Furthermore, there was no differential impact of the response deadline on reaction times ($F<1$) or accuracy ($F(1,45)=2.019$, $p=0.162$, $\eta p^2=0.043$) for reward compared to non-reward anticipation (i.e., no interaction between experiment and reward).

However, for response omissions, there were more omissions (i.e., participants failed to provide a response within the response deadline) when enforcing strict (20.27%) compared to liberal (1.12%) response thresholds ($F(1,45)=513.411$, $p<0.001$, $\eta p^2=0.919$). Additionally, there was a significant interaction between response deadlines and (non-)reward anticipation ($F(1,45)=15.588$, $p<0.001$, $\eta p^2=0.255$) (see results Exp. 1 and Exp. 2).

In terms of CS excitability, there was a significant (four-way) interaction between action cue, motivational cue, stimulation epoch and response deadline ($F(1,45)=9.360$, $p=0.004$, $\eta p^2=0.172$), confirming

that the employment of liberal compared to strict response deadlines affects CS excitability differently (see results Exp. 1 and Exp. 2).

Discussion

In Exp. 2 faster responding was encouraged by the employment of a stricter response deadline using a trial-by-trial adjustment algorithm (Elchlepp & Verbruggen, 2017; Leiva et al., 2015). Behaviorally, reward prospect sped up reaction times. Most interestingly, reward anticipation was associated with increased CS excitability for Go responses during the early stimulation epoch and was then followed by an increase of CS suppression. An exploratory statistical comparison between both experiments confirmed that only the enforcement of time pressure upon individuals was associated with motivational modulations of CS excitability.

General Discussion

In two experiments, we examined preparatory CS excitability during (no) task preparation under different levels of time pressure. Both Exp. 1 and 2 revealed a behavioral effect of motivation on Go-trial reaction times. Our findings suggest that reward effects on CS excitability are dependent on the preparation of an actual action, as well as on temporal requirements (e.g., time pressure) invoked by the task.

Using a liberal response deadline (Exp. 1) was associated with no motivation-dependent CS excitability changes. In contrast, when employing a stricter response threshold (Exp. 2), CS excitability was modulated by cue-induced motivational states. This was mainly due to the fact that during the early stimulation epoch on Go trials, CS excitability was increased for reward compared to non-reward anticipation.

The results suggest that reward only alters CS excitability if the motivational cue is sufficiently rewarding. In other words, with liberal response thresholds (Exp. 1) reward may just loose its motivational effect to some extent as it is too self-evident to obtain the reward even if one is not performing optimally (e.g., by providing relatively slow responses). In contrast, setting stricter response thresholds (Exp. 2) may increase the motivation to perform more optimally, as the probability of receiving a reward strongly decreases if one is performing sub-optimally. We hypothesize that the

probability of receiving a reward is associated with a dopamine-dependent increase in rewards' motivational salience or 'wanting' (Berridge & Robinson, 1998, 2003). In primates, there are strong dopaminergic projections from midbrain areas to the dorsal premotor cortex (PMd), which contains one of the forebrains' highest amount of D1 receptors (Sawaguchi, 1997). Moreover, the neural activity of rodents' premotor cortex has been associated with motivational salience (Roesch & Olson, 2004) and with preparatory CS suppression in humans (Duque, Labruna, Verset, Olivier, & Ivry, 2012). Collectively, these findings may be parsimonious with the idea that motivational salience may affect the premotor cortex, which, in turn, biases CS excitability accordingly.

To our knowledge, this is the first time that a study compared the development of CS excitability during (no) action preparation directly. Both Exp. 1 and Exp. 2 revealed a task-dependent effect of stimulation time on CS excitability. CS suppression was only observed during Go trials, but was statistically absent during NoGo trials in both experiments. The absence of any time- or reward-dependent CS excitability changes during NoGo trials, may relate to two underlying processes. First, individuals may actively suppress any motor output, which resulted in CS excitability that was overall decreased but was not associated with any time- or reward-dependent CS excitability changes. Second, decreased but time- and reward-invariant CS excitability may be due to the fact that individuals, as instructed, did not prepare for any action. Given the

current paradigm, it is not possible to distinguish between both alternatives. Therefore, future research needs to identify whether the non-preparation of an action compared to the active inhibition of motor output modulates CS excitability differently when no response is to be made.

Changes in preparatory CS excitability could reflect one of three underlying mechanisms that are, however, not necessarily mutually exclusive. First, preparatory CS suppression could reflect a process of competition resolution, thereby modulating the excitability-inhibition balance between non-selected and selected muscles (Duque et al., 2017; Duque et al., 2012; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010). This interpretation, however, mainly comes from studies that examined preparatory CS excitability when individuals were informed about the upcoming response. The fact that preparatory CS suppression is also observed when the cue was uninformative about the upcoming relevant response is difficult to reconcile with the competition resolution account, as it is unknown which effector should be suppressed or promoted among multiple alternatives. Second, preparatory CS suppression may reflect an impulse control mechanism that helps to avoid premature movement (Duque et al., 2017; Duque et al., 2012; Duque et al., 2010). Impulse control may specifically be associated with PMd. Duque and colleagues (2012) found that preparatory CS suppression was attenuated for a selected effector when preceded by repetitive TMS (rTMS) over PMd compared to when PMd was unaffected by the

virtual lesion that rTMS induces. In contrast, preparatory CS excitability remained unchanged for a non-selected effector, which suggests that PMd is involved in impulse control over selected effectors. The current may be in line with the impulse control account. However, it was proposed that impulse control inhibits already selected responses at the spinal level (Duque et al., 2012), which again would not fit with the current results as we observe preparatory CS suppression even though there was no information available pertaining the specificity of the upcoming response. Potentially most parsimonious with the current results is the third account, which proposes that CS suppression reflects a form of gain modulation (Greenhouse et al., 2015; Hasbroucq et al., 1997). Greenhouse and colleagues (2015) conceptualized suppression as a spotlight with a context-dependent aperture targeted at the selected response representations. In a simple context the aperture is broad, whereas it becomes narrower in a choice context. Consequently, the narrower focus in a choice context would increase the signal-to-noise ratio of response options resulting in a higher probability of being selected due to improved sensitivity to excitatory inputs. Consequently, reward-induced heightened CS excitability as observed for the early stimulation epoch in Exp. 2 may actually reflect an initial broadening of the aperture of the spotlight, which would speak to a nonspecific motivational effect (e.g., motivational salience) onto the motor system. Such broadening of the spotlight's aperture, however, would be associated with a decreased signal-to-noise ratio

and impaired sensitivity to excitatory inputs. Although counterintuitive at first, it has indeed been shown that reward may have detrimental effects on information processing. For example, it was reported that rewarded-stimulus features capture attention even when the deployment of attentional resources towards such features was counterproductive (Hickey, Chelazzi, & Theeuwes, 2010). Although there may be preliminary indications for a detrimental effect of reward, which may be associated with (early) changes in the motor system, further research is needed to scrutinize such claims (see also Notebaert & Braem, 2015). Following an initial CS excitability increase (Exp. 2), the current results showed stronger CS suppression for reward compared to non-reward anticipation. Assuming that CS suppression may reflect increased signal-to-noise, reward may help to reduce intrinsic neural noise (Manohar et al., 2015) resulting in stronger CS suppression.

In conclusion, the present results show that CS excitability is modulated by reward, but that this modulation may be contingent upon distinct task-factors such as time pressure. Accordingly, it is of utmost importance to take these factors into account when comparing different findings or aiming to replicate results.

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CHAPTER 6

NO EVIDENCE OF REWARD PROSPECT MODULATING SHORT INTRACORTICAL INHIBITION DURING ACTION PREPARATION

Action preparation is associated with corticospinal (CS) suppression prior to target onset and it has recently been shown that this suppression is modulated by the prospect of reward. However, CS suppression may be due to decreased excitation, increased inhibition, or both, which is impossible to distinguish using single-pulse transcranial magnetic stimulation (TMS). To examine inhibitory influences during action preparation contributing to changes in CS excitability, a rewarded cue-target delay paradigm was employed in which a cue indicated whether reward could be obtained for fast and accurate target responses. Thereafter, a delay period followed in which CS excitability or short intracortical inhibition (SICI) was examined via application of single- or paired-pulse TMS over the left primary motor cortex (M1). Subsequently, a circle (i.e., target) appearing left or right from fixation required participants to provide a left or right index finger response, respectively. To examine CS excitability and inhibitory mechanisms associated with reward prospect during action preparation,

electromyography (EMG) was obtained from the right first dorsal interosseous (FDI) muscle. Results revealed that reward improved behavioral performance and was associated with changes in CS excitability. However, SICI was not modulated by reward prospect. These findings may tentatively suggest that reward-related changes in CS excitability are not associated with intracortical inhibitory processes.

INTRODUCTION

The preparation of a task or an action permits humans to anticipate future events and demands in a flexible manner (Bode & Haynes, 2009; Brass & Von Cramon, 2002, 2004). Using transcranial magnetic stimulation (TMS) and concurrent electromyography (EMG) revealed that the preparation of motor output is associated with changes in corticospinal (CS) excitability (Duque & Ivry, 2009; Greenhouse, Sias, Labruna, & Ivry, 2015b; Lebon et al., 2015). Typically, during a cue-target delay paradigm, a cue indicates which response to be made after an imperative signal (i.e., target onset), while preparatory CS excitability is assessed during the delay period. TMS applied over the primary motor cortex (M1) has shown that preparatory CS excitability for the task-relevant effector is usually suppressed relative to baseline CS excitability (e.g., Duque & Ivry, 2009). However, it has also been shown that task-irrelevant effectors show suppression (Greenhouse et al., 2015b) and suppression even occurs after (effector) uninformative cues (Bundt, Abrahamse, Braem, Brass, & Notebaert, 2016; Duque & Ivry, 2009). Although there is some controversy about the functional role of such preparatory CS excitability changes (for a review, see Duque, Greenhouse, Labruna, & Ivry, 2017), it has been shown that reward prospect modulates preparatory CS excitability in a time dependent fashion (Bundt et al., 2016). Specifically, we showed that early after the onset of a reward compared to a non-reward cue CS excitability was increased and

decreased just before target onset. However, it remains a major challenge to interpret these outcomes in the light of methodological limitations that are associated with the assessment of CS excitability using single-pulse TMS over motor areas. Specifically, CS excitability that is assessed via motor-evoked potentials (MEPs) and concurrent surface EMG is the net result of a mixture of various potentially contributing processes that may originate from several distinct brain regions. Thus, given its broad focus, the application of TMS over the motor cortex stimulates not only CS neurons, but also affects various fibers projecting to CS neurons. These fibers can originate from within M1, but may also originate from premotor or somatosensory areas, as well as from subcortical brain regions like, for instance, the thalamus (Duque et al., 2017). In addition, MEPs are also dependent on the excitability within the CS tract, which modulates the strength of CS neurons projecting to motoneurons. To determine the role of the contributions to reward-modulated CS excitability, it is necessary to identify and distinguish between each (potential) factor contributing to MEP amplitude. For instance, short inctracortical inhibition (SICI; Kujirai et al., 1993) represents a likely mechanism affecting MEP amplitude. SICI is examined by applying a suprathreshold condition pulse and a suprathreshold test pulse through the same coil over the motor cortex. In essence, the conditioning stimulus inhibits the test MEPs at short interstimulus intervals (~<=5 ms). It is assumed that SICI is generated by

interneurons within the M1 through synaptic inhibition mediated through the gamma-aminobutyric acid A receptor (GABAA).

Interestingly, SICI has been found to be reduced during the foreperiod of a warned reaction time (RT) task (Sinclair & Hammond, 2008, 2009) and during the delay of a cue-target delay task (Duque & Ivry, 2009). However, intracortical inhibition has also been found to increase during the voluntary inhibition of prepared actions (Coxon, Stinear, & Byblow, 2006).These findings suggest that intracortical inhibition may represent a candidate mechanism to be at play, contributing to CS excitability changes during action preparation. To that end, the current study was designed to explore whether the effect of reward-prospect on CS excitability could be associated with intracortical circuits modulating the MEP amplitude. To examine potential reward-related effects on intracortical inhibition, we employed a cue-target delay paradigm in which a motivational cue was presented (300 ms) indicating whether reward could be obtained on current trial for fast and accurate target performance. Thereafter, a delay period followed (600 ms), which was succeeded by a circle appearing left or right from fixation (i.e., target) upon which individuals were asked to provide a left or right index finger response, respectively. Throughout the delay period, single- or paired-pulse TMS was applied either early (i.e., 400 ms after motivational cue onset) or late (i.e., 800 ms after motivational cue onset) over the left M1 and EMG was recorded using surface electrodes from the right first dorsal interosseous (FDI) muscle. Single-pulse TMS was aimed

at examining CS excitability, whereas paired-pulse TMS was employed to assess SICI during action preparation. It was predicted that reward prospect compared to non-reward prospect resulted in decreased CS excitability and thus invigorates preparatory CS suppression. Furthermore, we were interested to explore whether reward prospect is associated with changes in intracortical inhibition, and, specifically, whether SICI was modulated by reward prospect during action preparation.

METHODS

Participants

Twenty-one participants took part in the experiment. All participants provided their written informed consent prior to the experiment and were prescreened for neurological or psychiatric disorders that may have prohibited a safe application of TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Participants were monetarily compensated for their participation (£15) and could have obtained additional performance-contingent reward (max. £10). The study was performed in line with the declaration of Helsinki and according to the ethical guidelines of the University College London Institute of Neurology (London, UK).

TMS stimulation and EMG recordings

Single- and paired-pulse TMS was applied via a figure-of-eight coil connected to two Magstim 200 units (Magstim, UK). TMS was applied over left primary motor cortex above the "motor-hotspot" that elicited reliable MEPs of the largest amplitude. To ensure correct coil placement, the position of the location eliciting reliable MEPs was marked and throughout the experiment the coil was hand-held above this location by the experimenter. The coil was positioned tangentially to the surface of the scalp and perpendicularly to the central sulcus.

Single-pulse TMS intensity was determined jointly for the FDI and the abductor digiti minimi (ADM) muscle at rest and was specified as the stimulator intensity that evoked MEP amplitudes of 1 mV in 50% of stimuli. On average, this led to a pulse intensity of M=62.2% ± SD=6.3% of the maximum stimulator output.

To examine SICI, a paired-pulse TMS protocol was employed comprising a subthreshold conditioning pulse inhibiting underlying cortical areas that was followed after 2 ms by a suprathreshold test pulse. To specify the stimulation intensity of the conditioning pulse, individuals were asked to maintain an isometric contraction of the FDI (~10% of maximal voluntary contraction), during which the TMS pulse intensity was determined that evoked a MEP amplitude of 1 mV in 50% of stimuli (i.e., active motor threshold; aMT). On average, the aMT was M=48.1% ± SD=5.1% of the maximum stimulator output. The conditioning pulse intensity was eventually set to 80% of the aMT. The suprathreshold test pulse intensity was equal to the spTMS intensity (see above).

Throughout the experiment, EMG was measured from the right FDI and ADM muscle of the hand using surface electrodes (please note that the current paper focusses on the FDI only).

Stimuli and procedure

Participants were seated in a comfortable chair in front of a computer screen with an eye-monitor-distance of ~60 cm. Manual responses were provided on a QWERTY keyboard that was turned by

180°, i.e., with the function keys facing the participant (c.f., Bundt et al., 2016; Klein, Olivier, & Duque, 2012; Klein, Petitjean, Olivier, & Duque, 2014). Participant's left and right index finger tips were placed on the keyboard between the F8 and F9, and F4 and F5 buttons, respectively. When executing a response, participants performed an abduction movement towards the medial response keys (i.e., left finger abduction movement towards the the F8 key, or a right index finger abduction movement towards the F5 key) and pressed the respective button eventually.

In the present experiment, participants could obtain extra monetary reward for fast and accurate target performance (max. £10). Visual feedback was provided throughout the experiment in terms of a progress bar presented in the upper fourth of the computer monitor representing the already accumulated reward relative to the total amount of reward that could be obtained throughout the experiment.

Each trial started with the presentation of a pre-cue fixation asterisk presented in the center of the screen for 500 ms (see Fig. 1 for a schematic illustration of the trial procedure). Subsequently, a motivational cue was presented for 300 ms above fixation, indicating whether reward (+1) or no reward (+0) could be obtained on the current trial for fast and accurate performance. Another fixation period followed for 600 ms (i.e., delay period) within which single- or paired-pulse TMS (spTMS; ppTMS) could be applied during two different time epochs (see below). Thereafter, a circle left or right from fixation was presented (i.e., target) and participants were asked

to respond to this target with a left or right index finger response, respectively. The time individuals had to respond to the target was determined by an adaptive tracking procedure. This algorithm subtracted 25 ms from the response deadline (and therefore from the duration of target presentation) when the participant provided three successively correct responses in time, and added 25 ms to the response deadline when the participant provided an erroneous response or did not respond in time (c.f., Elchlepp et al., 2017; Leiva et al., 2015). After participants provided an accurate response within the allowed time window, a fixation period followed for 200 ms and was then replaced by a feedback screen for 1000 ms. The feedback screen consisted of the presentation of a grey-colored "+1" or "+0" above fixation, indicating that reward or no reward has been obtained on current trial, respectively. If the target response was erroneous or the participant did not provide a response within the allowed time window, these numbers were replaced by "wrong" or "too late" above fixation. At the end of each trial, the progress bar indicating the already accumulated reward was updated. Each trial was separated from the next trial by a randomly jittered inter-trial interval of 900 – 1100 ms.

TMS was applied during three different timings. First, to examine baseline CS excitability (spTMSbaseline), TMS was applied 200 ms before motivational cue onset. Second, to examine CS excitability throughout the delay period, TMS was applied either 400 ms (spTMSearly) or 800 ms (spTMSlate) after motivational cue onset.

Third, to probe SICI throughout the delay period, a suprathreshold test pulse that was preceded by a subthreshold conditioning pulse by 2 ms was applied 400 ms (SICIearly) or 800 ms (SICIlate) after the onset of the motivational cue.

In total, the experiment consisted of 704 trials divided into five blocks that were each separated by a 30 s break. The first block (32 trials) served as practice block for the participants to become familiar with the task and did not include any TMS. The subsequent four blocks (168 trials each) comprised the experimental blocks and included the application of TMS. In total, each of the experimental block comprised eight trials of spTMSbaseline and 128 trials of TMS applied during the delay period, which comprised an equal amount of spTMSearly, spTMSlate, ppTMSearly, and ppTMSlate. The remaining 32 trials within one experimental block did not include any TMS. Each experimental block consisted of an equal amount of randomized trials that were balanced across responses (left, right FDI) and motivational cue (reward, non-reward).

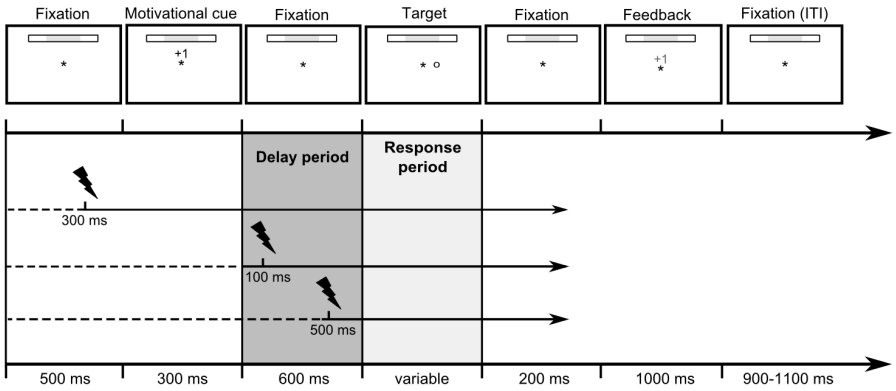

Fig 1. Schematic illustration of the trial procedure. See the main text for a detailed description of the procedure.

Data analysis: behavior

The behavioral analysis was based on trials that did not include any TMS stimulation, as it has been shown that the application of TMS over motor areas could distort subsequent behavioral performance (Hasbroucq, Kaneko, Akamatsu, & Possamaï, 1997). Trials were controlled for premature (RT < 100 ms) and late (RT > target duration) responses. Furthermore, the behavioral analysis included only correct trials that were preceded by correct responses on the previous trial. RTs and the percentage of correct trials were submitted to paired-sample t test with non-reward cue and reward cue as variables.

Data analysis: CS excitability and SICI

Continuous EMG activity was recorded using Signal software (Cambridge electronic design, Cambridge, England) and exported for offline analysis. An automatized algorithm detected the peak-to-peak amplitude of MEPs following TMS within a time window between 20-40 ms succeeding the pulse. Trials were controlled for background EMG activity within a time window of 100 ms preceding the TMS pulse. The trial was rejected from further analysis if the root mean square of the background activity was on average larger than 100 μV. Trials that were preceded by or included an erroneous response or that included a premature response (RT < 100 ms) on the target were excluded from further analysis as well. Furthermore, outlier (Grubbs test, $p<0.05$) and small amplitude (< 50 μV) MEPs were discarded.

To analyze CS excitability changes, the average of absolute MEP amplitudes (in mV) were submitted to a repeated measures ANOVA (rANOVA) with motivational cue (reward, non-reward) × stimulation epoch ($spTMS_{early}$, $spTMS_{late}$) as within subjects factor.

The percentage of SICI (%SICI) was calculated using the formula "$[1-(MEP_{conditioned}/MEP_{unconditioned})]\times100$", which expresses the average amplitude of conditioned MEPs relative to the average amplitude of non-conditioned MEPs (Coxon et al., 2006). Thus, 100% inhibition would illustrate the abolition of the unconditioned CS response, whereas 0% inhibition would reflect no effect of the conditioning pulse on the CS response. Averaged SICI was submitted

to a rANOVA with motivational cue (reward, non-reward) × stimulation epoch ($SICI_{early}$, $SICI_{late}$) as within subjects factor.

Please note that after the first half of the experimental blocks the stimulation intensity of the test pulses could be adjusted on an individual basis. This resulted in generally larger CS excitability (see results). This was done to account for different levels of CS excitability during ppTMS that may have influenced the degree to which the conditioning pulse inhibited CS excitability. In the analysis below, however, we do not compare the first and the second experimental part with each other, but examine CS excitability and SICI separately. Thus, the analysis of CS excitability and SICI were both performed for the first and second part individually. All statistical analyses were performed using SPSS statistical software (Version 22.0. Armonk, NY, USA: IBM Corp.).

RESULTS

Behavior

Reaction times were significantly faster during trials including reward compared to non-reward prospect in both the first (365 ms vs. 374 ms; $t(20)=2.872$, $p=.009$) and second (356 ms vs. 363 ms; $t(20)=2.527$, $p=.020$) experimental part.

Similarly, the percentage delayed responses was lower on trials promising reward compared to non-reward in the first (22.3% vs. 31.6%; $t(20)=4.387$, $p<.001$) as well as in the second experimental part (22.3 vs. 35.5%; $t(20)=4.656$, $p<.001$).

Neither for the first, nor for the second experimental part was the percentage of correct responses statistically different during trials promising reward compared to non-reward (99.8% vs. 99.9%, and 99.7% 99.9%, respectively; ts<1).

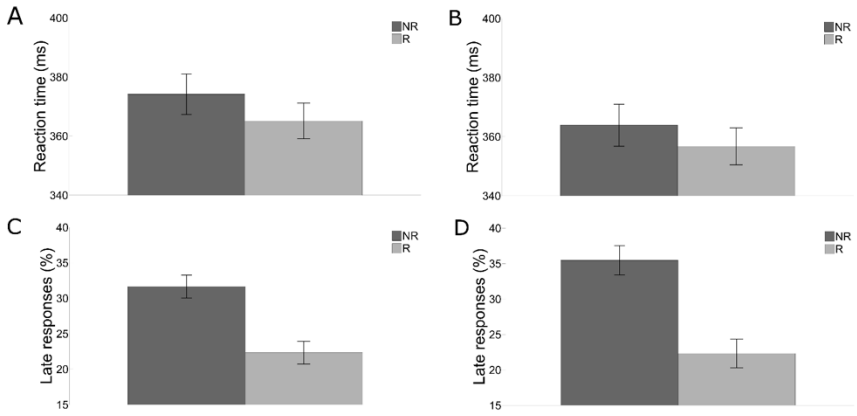

Fig 2. Behavior. The plots in the upper part show the averaged reaction times for the first (A) and second (B) experimental part. The plots in the lower part show the mean percentage of missed responses for the first (C) and second (D) experimental part. Error bars indicated one SEM.

CS excitability and SICI

The analysis of CS excitability for the FDI during the first experimental part revealed less CS excitability during reward compared to non-reward prospect (1.19 mV vs. 1.26 mV; $F(20)=7.565$, $p=.012$, $\eta p^2=.274$). Furthermore, CS excitability was larger during early compared to late stimulation epochs (1.30 mV vs. 1.15 mV) indicating that CS excitability decreased throughout the delay period ($F(20)=6.279$, $p=.021$, $\eta p^2=.239$). However, there was no interaction between both factors ($F<1$).

The CS excitability analysis for the FDI during the second experimental part, however, did only show a significant main effect of stimulation epoch, again indicating larger CS excitability during early compared to late epochs (1.404 mV vs. 1.220 mV; $F(20)=17.6$, $p<.001$, $\eta p^2=0.468$). There was neither a main effect of reward (reward= 1.31 mV vs. non-reward= 1.32 mV) nor a significant two-way interaction between both factors (Fs<1).

The analysis of SICI during the first experimental part did not reveal any effects of (non-) reward prospect on intracortical inhibition (reward=38.17% vs. non-reward=39.68%; $F<1$). However, results indicated a main effect of stimulation epoch, illustrating increased inhibition early compared to late within the delay period (43.55% vs. 34.3%; $F(20)=4.647$, $p=0.043$, $\eta p^2=0.189$). However, there was no interaction between both factors ($F<1$).

The analysis of SICI during the second experimental part, did not yield any statistically significant main or interaction effects (Fs<1).

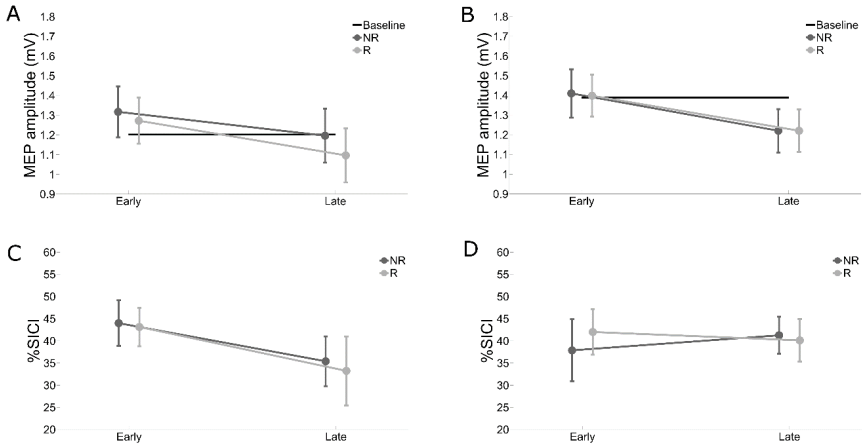

Fig. 3 CS excitability and SICI. The plots show CS excitability changes during the first (A) and second (B) experimental part. The black bar illustrates baseline CS excitability. In the lower panel, %SICI during the first (C) and second (B) experimental part is represented. Error bars indicate one SEM.

DISCUSSION

Reward prospect has been found to modulate CS excitability during action preparation (Bundt et al., 2016). Specifically, it was reported that CS responses are stronger suppressed during reward compared to non-reward prospect. Changes in preparatory CS suppression that are examined using spTMS, however, may be due to decreased CS excitability, increased inhibition, or both. The present study explored whether reward-related changes of inhibitory mechanisms are associated with reward-related changes in CS excitability. To examine preparatory CS excitability, spTMS was applied within the delay period during a rewarded cue-target delay task. To assess preparatory inhibitory mechanisms, SICI (Kujirai et al., 1993) was examined by means of a ppTMS protocol within the delay period. Although results revealed reward-related changes in CS excitability (during the first experimental part), no effect of reward prospect on SICI was obtained. These findings may tentatively suggest that reward-related changes in CS excitability are due to reduced excitation of the CS tract and are not associated with intracortical inhibitory processes.

Preparatory CS excitability is typically suppressed throughout the delay period of a cue-target delay task in anticipation of a response (Duque & Ivry, 2009; Greenhouse, Saks, Hoang, & Ivry, 2015a; Greenhouse et al., 2015b; Lebon et al., 2015). In a previous study, we have shown that CS excitability is modulated by the prospect of

performance-contingent reward (Bundt et al., 2016). The current findings are generally in line with the previous results as they indicate decreased CS excitability during reward compared to non-reward prospect. However, previous findings suggested time- and reward-contingent changes of CS excitability such that during prospect of reward compared to non-reward, CS excitability increased early after motivational cue onset and was succeeded by steadily decreasing CS excitability, peaking just before target onset. The current results, however, did not yield time-dependent changes of reward-modulated CS excitability. Instead, we observed overall decreased CS excitability during the prospect of reward compared to non-reward that was independent from the moment at which CS excitability was examined (during the first experimental phase only). The difference in CS excitability between previous and current findings may be explainable by task differences. In the previous study, we employed a Simon task (Simon, 1969), whereas in the current study, a simple choice reaction time task was employed. Furthermore, we have also observed that the early reward effect on CS excitability becomes more pronounced when individuals were forced to strongly engage in a task by employing a strict (compared to a liberal) time-out procedure (i.e., response deadline) on Go responses in a Go/NoGo task (unpublished results). Thus, the degree to which individuals engage in the preparation of a motor response may explain the early (ambiguous) effects of reward on CS excitability. Future research needs to examine the effect of task

differences on (early) preparatory CS excitability. Alternatively, the difference in CS excitability between previous and current findings may point to distinct (but not necessarily mutually exclusive) mechanisms that are at play early and late during a preparatory delay period. For example, the initial increase of CS excitability during reward prospect in our previous study may reflect individuals' motivation to obtain the presented reward (e.g., motivational salience; Berridge & Robinson, 1998, 2003), whereas late in the delay period CS excitability may reflect actual preparation of motor output. However, this discussion is speculative and future research needs to clarify whether preparatory CS excitability changes throughout the delay period reflect distinct mechanisms.

Reward-related changes in preparatory CS excitability may be due to changes of excitability, inhibition or both. The present study aimed to distinguish between these possibilities by exploring whether reward-related changes of preparatory CS excitability are associated with changes in inhibitory circuits (i.e., SICI). Previous research reported that inhibition is reduced during the foreperiod of a warned RT task (Sinclair & Hammond, 2008, 2009) and during the delay of a cue-target delay task (Duque & Ivry, 2009). However, intracortical inhibition has also been found to increase during the voluntary inhibition of prepared actions (Coxon et al., 2006). Furthermore, there is also some evidence suggesting an increase of SICI during reward anticipation (Kapogiannis, Campion, Grafman, & Wassermann, 2008) and reward perception (Thabit et al., 2011). The

present results, however, did not yield such a reward-related effect of SICI. One explanation of why SICI was not modulated by reward prospect relate to task differences between the current findings and the observations made by Kapogiannis et al. (2008) and Thabit et al. (2011). In both previous studies, SICI was not measured within the interval during which individuals prepared motor output and, therefore, reward was not contingent on behavioral performance and the sufficient preparation thereof. This may allude to the possibility that the actual preparation of reward-contingent motor output has different (and to some extent overruling) effects on inhibitory circuits compared to non-preparatory reward anticipation or perception.

Although, the present results did not reveal any effect of (non-) reward prospect on intracortical inhibitory mechanisms (i.e., SICI), results indicated that SICI decreases across the preparatory period. While this finding may be in line with previous reports suggesting reduced inhibition possibly associated with motor preparation (Davranche et al., 2007; Duque & Ivry, 2009; Sinclair & Hammond, 2008, 2009), it must be stressed that in the current study CS excitability decreased throughout the delay period as well. Thus, the conditioning pulse that is necessary to obtain SICI, may have acted on different levels of motor excitability, which may have led to an inflation of SICI. Therefore, one needs to be cautious in interpreting the apparent but statistically weak effect of stimulation epoch on SICI in the current study.

To conclude, the present study shows reward-related changes in preparatory CS excitability, but no changes of reward-related inhibitory mechanisms during a cue-target delay task. These findings may suggest that in the current task changes in preparatory CS excitability may not be associated with intracortical inhibitory processes.

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CHAPTER 7

GENERAL DISCUSSION

The present doctoral dissertation investigated to what extent the motor system and specifically M1 with its CS output is subject to automatic influences and decision-related variables that bias action preparation.

How and whether CS excitability is modulated by task- and response-irrelevant visual input was examined in **chapter two.** Colored-circle stimuli or spatial (non-)words were presented and individuals were asked to respond with a left/right index finger button press to the former, while not responding at all to the latter. During the presentation of (non-)words, CS excitability was examined. Intriguingly, we observed a CS excitability congruency effect, which was indicated by increased CS excitability when the stimulated M1 controls the FDI that was congruent with the semantics of the spatial word (e.g., the word left and left FDI), and relatively decreased CS excitability when the FDI controlled by the stimulated M1 was incongruent with the spatial concept (e.g., the word left and right FDI). These results were taken as evidence that the assumption of cognition being grounded in sensorimotor systems does not only hold for relatively specific action words (Hauk, Johnsrude, & Pulvermüller, 2004; Hauk & Pulvermüller, 2004), but

may also be true for relatively abstract (spatial) concepts. Furthermore, and more importantly for the remainder of the dissertation, these results showed that the motor system could be modulated by external and task-irrelevant stimulus features (such as the spatial semantics) in a non-deliberative (i.e., automatic) fashion. If and how the motor system is biased by external factors that do not (or only indirectly) relate to actual movement execution was investigated in the following chapters.

We were interested to examine whether the extent to which action preparation modulated CS excitability could be influenced. Motivation and specifically reward is one of the major incentives that influence and drive human behavior. In a series of studies, we investigated whether the prospect of receiving performance-contingent reward versus the prospect of not receiving performance-contingent reward changes the amount to which action preparation as well as execution affects the motor system. In **chapter three**, we employed a rewarded cue-target delay Simon task. CS excitability was assessed throughout the cue-target delay period as well as just after the onset of the target (Simon) stimulus. Although reward did not change the size of the behavioral congruency effect, we observed that CS excitability was modulated by the prospect of receiving a reward in a time-dependent fashion throughout the cue-target delay period. CS excitability was unaltered, however, when the motivational cue indicated that no additional reward could be obtained. Taken together, the results from chapter three indicate that

reward does not alter the size of the behavioral congruency effect in the Simon task and neither the amount of CS excitability early after target onset. However, the results suggest that preparatory CS excitability throughout the delay period is heavily biased by reward prospect in a time-dependent fashion.

Chapter four was designed to corroborate and extend the findings described in chapter three. We replicated the design from chapter three but utilized Stroop stimuli as targets. In contrast to the findings from chapter three, results did not reveal any significant effect of reward-dependent CS excitability throughout the cue-target delay period and neither after target onset. However, results showed that the size of the behavioral Stroop congruency effect was modulated by reward, which was especially true for slower reaction times.

Chapter five was designed to investigate the unexpected finding that preparatory CS excitability during reward prospect (in chapter three) was increased (relatively to CS excitability during non-reward prospect) shortly after the onset of the motivational cue. In this chapter, we tried to pinpoint whether this initial CS excitability increase was due to the prospect of reward itself (e.g., motivational saliency) or whether it was contingent on the preparation of an action. Two experiments were performed to examine these questions. While the first experiment imposed only little time pressure on individuals, experiment two imposed a more demanding response regime upon individuals. Results of the first experiment did

not show an effect of reward on CS excitability. Experiment two, in contrast, revealed initially heightened CS excitability during the prospect of reward for Go responses, while there was no such effect for NoGo responses. Thus, these results may suggest that the anticipation of reward does not modulate CS excitability per se, but depends on the more fundamental decision process whether one needs to prepare a response at all.

Finally, **chapter six** examined whether the previously observed reward-related changes of CS excitability are associated with changes in inhibitory circuits. To that end, CS excitability and short intractortical inhibition (SICI) were examined during action preparation. Results showed that CS excitability was altered during reward compared to non-reward anticipation, whereas no changes in SICI were observed. These findings may tentatively indicate that reward-related preparatory CS suppression is due to changes in CS excitability, but are not associated with corticocortical inhibition.

To conclude, the present dissertation indicates that M1 and its CS output are modulated by processes that are not (or only indirectly) related to mere action execution or the breakdown of complex movements. Instead, M1 and its CS output seem to reflect decision-related information processing that bias action preparation and execution.

Control and automatic activation

It was argued that cognitive control allows us to keep automatic effects influencing our cognitive system in check. Conflict arising in information processing systems may be due to an overlap between stimuli and responses features, resulting in the automatic activation of response codes via a direct route, while appropriate response selection is implemented via an indirect route (Eimer, 1995; Eimer, Hommel, & Prinz, 1995; Kornblum, Hasbroucq, & Osman, 1990). In the first empirical chapter of the present dissertation, automatic effects on the motor system were observed, although i) the stimuli (during which CS excitability was examined) did not require any motor response, and ii) there was no simultaneous overlap between stimuli and response features (i.e., the presented stimulus comprised a semantic feature only).

Generally, these findings emphasize the strength of automatic processes. Even though stimuli were never associated with any response, CS excitability was differentially modulated by the semantics of the stimulus. This may have happened via a fast and direct route (Eimer, 1995; Eimer et al., 1995; Kornblum et al., 1990) but the current findings are difficult to ascribe to an overlap between stimulus and response features due to the simple fact that the semantic stimulus during non-response trials did not convey any response feature. One viable alternative interpretation of the findings, however, may be that stimulus and response features do not need to overlap at the same time. In other words, response codes may

be transferred and activated by stimulus features across trials. Accordingly, it may be sufficient for automatic activation of response codes if the semantic feature of the stimulus in trial 1 shares response features with the stimulus in trial N-1 (i.e., the automatic effect in trial 1 is triggered by the stimulus-response coding in trial N-1). Indeed, previous work indicated that response discrimination in working memory is necessary for automatic motor activation (Ansorge & Wühr, 2004, 2009; Hommel, 1996; Wühr & Ansorge, 2007; Zhao, Chen, & West, 2010). For example, Ansorge and Wühr (2009) observed a Simon effect for unimanual detection responses (on Go trials during a GoNoGo task) only if it was preceded by a choice-response task, which suggests that response discrimination transfers across trials and even across tasks. These findings may suggest that cognitive control is only partly able to control automatic influences. However, future studies need to further investigate to what extend this is true. To that end, our paradigm provides an adequate design to build upon and to examine whether, for example, automatic activation occurs when response discrimination in working memory is eliminated (e.g., by omitting the Go trials altogether).

Preparatory control

Braver (2012) proposed a dual-mode cognitive control framework that distinguishes between proactive and reactive control. In this framework, proactive control selects and maintains goal-relevant information in order to optimally bias perception and action

systems before action, while reactive control is supposed to be engaged only if there is an actual need for the deployment of control. The dual-mode framework predicts that proactive control is associated with sustained activation of lateral prefrontal cortex (PFC), whereas reactive control is accompanied by transient lateral PFC activation. Interestingly, it has been shown that in a high-load working memory task, performance-contingent reward resulted in behavioral improvements and in a shift towards proactive control (Jimura, Locke, & Braver, 2010). This shift towards a proactive control mode was reflected by an increase of sustained and anticipatory activity in dorsolateral PFC. The findings of the present dissertation (as well as previous findings) may be in line with this framework and specifically with the conceptualization of proactive control in the sense that CS excitability during a preparatory period may be a reflection of proactive control mechanisms. Specifically, decreased CS excitability during the preparation of a response that is associated with reward (compared to non-reward) may reflect a similar shift towards a more proactive control mode as previously proposed (Jimura et al., 2010). Interestingly, Jimura et al. (2010) found that highly reward sensitive individuals showed a more prominent shift towards a proactive control mode. Correspondingly, interindividual differences in trait reward sensitivity may be an important aspect to control for when examining preparatory CS excitability during reward anticipation.

Models on preparatory corticospinal suppression

The functional relevance of preparatory CS suppression remains ambiguous to date. Predominantly three, not mutually exclusive models have been proposed in an effort to explain preparatory CS suppression. This paragraph elaborates on each of these models on preparatory CS suppression and aims to integrate the results from the present dissertation with each theoretical framework.

The competition resolution hypothesis assumes that goal-directed behavior is associated with the discrimination between wanted and unwanted actions. Selecting among action alternatives requires the system to give priority to one action alternative over the other. Prioritization can occur via an independent "race" between action alternatives (Brown & Heathcote, 2008) but may also be the result of interactions between action alternatives (Usher & McClelland, 2001). The competition resolution hypothesis adopts the latter approach, assuming that CS suppression is due to reciprocal competitive and inhibitory interactions between representations of action alternatives. Indeed, TMS studies have shown CS suppression for nonselected effectors in choice RT tasks (Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000). The competition resolution hypothesis predicts, however, that only effectors and their associated action representation competing for action should show preparatory suppression (e.g., left versus right index finger if the task was to chose between a left and right index finger response). Thus, other muscles

that are task-irrelevant should remain unaffected by the competitive process between (potentially) task-relevant motor representations. This prediction, however, was refuted by several studies showing preparatory CS suppression for muscles that were irrelevant for the task at hand (Duque, Labruna, Cazares, & Ivry, 2014; Greenhouse, Saks, Hoang, & Ivry, 2015a; Greenhouse, Sias, Labruna, & Ivry, 2015b). Moreover, preparatory CS suppression was also reported for the effector involved in the forthcoming response, which is difficult to integrate with the assumption that the selected action representation inhibits the nonselected muscle representation (Duque, Labruna, Verset, Olivier, & Ivry, 2012; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010). Collectively, these findings suggest a rather broad inhibitory mechanism during action preparation and do not equivocally support the assumption of a reciprocal competition between action representations through mutual inhibition.

The finding that preparatory CS suppression in a delayed response task was stronger for selected compared to nonselected effectors gave rise to the second hypothesis about the functional relevance of preparatory CS suppression: the impulse control hypothesis. Because such findings were difficult to integrate with a mere reciprocal competition between action alternatives aiding goal-directed action selection, it was hypothesized that action preparation may be subject to two inhibitory processes: a broad (effector-unspecific) signal suppressing the motor system, and an effector-specific inhibitory signal, which safeguards the selected effector from

premature action execution. The existence of an inhibitory signal shielding the selected effector from premature action execution could enable other brain regions to engage in the preparation of these actions without running the risk of triggering accidental movement via excitatory processes (Cohen, Sherman, Zinger, Perlmutter, & Prut, 2010).

The third hypothesis assumes that preparatory CS suppression is the result of some gain modulation of the motor system. This gain modulation hypothesis was nourished by the finding that CS suppression was observed in the absence of choice in both task-relevant and task-irrelevant effectors (Greenhouse et al., 2015b). In this context, preparatory motor inhibition that acts globally increases the signal-to-noise ratio, because it helps to decrease the noise within the motor system (through inhibition) such that excitatory inputs "better stand out against a quiescent background" (Duque, Greenhouse, Labruna, & Ivry, 2017, p. 231). Although it is unknown whether such gain-modulation mechanism exists in mammals, it has been found to exist in primitive form in the leech motor system (Baca, Marin-Burgin, Wagenaar, & Kristan Jr., 2008). Greenhouse et al. (2015b) envisioned a spotlight-metaphor to explain how gain-modulation may be implemented and to account for the finding of stronger preparatory CS suppression in task-irrelevant muscle representations. Specifically, they described a spotlight with two features: spotlight position and spotlight aperture (Greenhouse et al., 2015b). The spotlight's position is determined by the selection of an

action representation. Positioning the spotlight over a specific action representation results in increased sensitivity of this action representation to excitatory inputs. The spotlight's aperture, in turn, affects the extent to which neighboring motor representations are affected by the spotlight's inhibitory role and location. The above-mentioned finding that CS suppression is largest for selected effectors can now be explained by means of the spotlight metaphor as the spotlight is typically positioned and strongest above the selected motor representation. Furthermore, the finding that also nonselected and task-irrelevant effectors show motor inhibition could now be ascribed to the aperture of such spotlight by means of a spillover of targeted inhibition. Indeed, it has been shown that motor inhibition (i.e., the aperture of such spotlight) is anatomically and/or functionally restricted and may dilate or contract depending on task demands (Duque et al., 2017).

The results from the present dissertation are difficult to reconcile with the competition resolution hypothesis. This is because the studies that were performed (and included in the present dissertation) involved a choice RT task whereby advance preparatory cues (i.e., motivational cue) were uninformative about the specificity of the forthcoming response. Despite of this unpredictability of the specific forthcoming response we have observed changes in CS excitability. According to the competition resolution hypothesis, however, CS suppression should not have been observed, because discriminating between action alternatives, thereby prioritizing one

action representation over the other as well as mutual inhibition was not possible.

Likewise, the impulse control perspective is also difficult to reconcile with the experimental design and results we have observed in the present dissertation. This is because impulse control has been interpreted as a process on top of (or in addition to) a process of competition resolution through mutual inhibition. In that sense, competition resolution needs to occur prior to any impulse control, which may not have happened in the experiments of the current dissertation. Furthermore, given the design of the experimental studies we have performed and the uninformativeness of preparatory (motivational) cues, it was not possible to distinguish between the effector that participants could have preferred over the other during action preparation. Thus, our experimental designs simply did not allow to examine impulse control of a single selected over a nonselected response. However, at least the impulse control account may be parsimonious with the present findings if one allows for a slightly broader perspective on the matter. Specifically, when an uninformative cue specifies two potential response alternatives, both alternatives (instead of a single one) may compete against all remaining action representations, which may result in the suppression of both action representations during uninformative cuing.

Nonetheless, the results of the present dissertation may be most parsimonious with the gain modulation account. In every paradigm

we have employed in the present dissertation to examine preparatory CS excitability, a motivational cue was presented that was uninformative about the forthcoming response (followed by a short delay period and target presentation). Despite the uninformativeness of the preparatory (motivational) cue, we have generally observed preparatory CS suppression. Finding preparatory CS suppression makes sense if one assumes that the individual generally prepares for all (of the two) possible action alternatives in order to implement fast and accurate behavior at target onset (similar to the argument made before). To that end, the spotlight centered at to-be selected action representations would explain inhibition irrespective of the informativeness of the preparatory (motivational) cue. The gain modulation account, however, envisioned only a single spotlight, which, in turn makes this account somewhat less intuitive and applicable to the present data when the functional or anatomical distance between action representations increases. Specifically, it remains to be tested whether gain modulation using a single spotlight could account for the inhibition of multiple action representations that are anatomically (or functionally) further apart (e.g., left index versus right index finger movement) and how this affects the spotlight's aperture (e.g., whether the spotlight accounts for more distant representations by simply increasing the aperture). A closely related question pertains to the neural substrates of preparatory inhibition as only little is known about the source and targets of CS suppression (Duque et al., 2017). For example, the preparatory motor

inhibition that was observed in the present dissertation might be due to intracortical, transcortical, subcortical, and/or spinal input. Teasing these cortical and spinal influences on the EMG signal (i.e., MEP amplitude) apart would be crucial for further examination of the characteristics of the gain modulation account and its proposed spotlight.

Reward and corticospinal excitability

Reward has been found to strongly guide behavior. To examine the neural underpinnings of reward processing, a wealth of studies has been conducted using functional magnetic resonance imaging (fMRI) to examine the brain's metabolic response to cues predicting performance-contingent (no) reward (Knutson, Westdorp, Kaiser, & Hommer, 2000). These experiments have identified subcortical brain regions such as the ventral striatum as well as the midbrain that show increased hemodynamic activity when the motivational cue predicts performance-contingent reward compared to when it predicts no performance-contingent reward (Knutson & Cooper, 2005; Schott et al., 2008). From these studies, however, it remains largely elusive if and how reward affects the motor system, and, specifically, M1 and its CS output. Only a few studies to date have examined CS excitability in response to reward (Bundt, Abrahamse, Braem, Brass, & Notebaert, 2016; Chiu, Cools, & Aron, 2014; Gupta & Aron, 2011; Kapogiannis, Campion, Grafman, & Wassermann, 2008; Klein, Olivier, & Duque, 2012; Mooshagian, Keisler, Zimmermann,

Schweickert, & Wassermann, 2015; Suzuki et al., 2014; Thabit et al., 2011; Vassena, Cobbaert, Andres, Fias, & Verguts, 2015). These studies, however, form a largely heterogeneous collection of experiments, comprising diverse paradigms, diverse stimulation protocols and timings as well as variable reward characteristics (e.g., primary versus secondary reward). This diversity of studies makes it difficult to interpret and integrate results across studies. The following paragraph, however, attempts to discuss and integrate this heterogonous pool of studies and findings examining the effect of reward on CS excitability.

It was shown, that urges for food and money (Gupta & Aron, 2011) as well as the anticipation of (primary) reward (Chiu et al., 2014) increase CS excitability before any action is taken. In an approach-avoidance-like task, Mooshagian et al. (2015) observed that CS excitability increased as a function of reward probability when individuals were required to approach (i.e., find) the target, while CS excitability was lower when the target needed to be avoided. Klein et al. (2012) showed that reward drives choices during action selection and that these reward-driven choices were accompanied by heightened CS excitability. In contrast, Thabit et al. (2011) did not find a reward modulation of CS excitability (i.e., MEP amplitude), but reported a reward-dependent modulation of SICI and SAI. Thabit et al. (2011), however, did not impose a reward-contingent motor response on participants. Likewise, Kapogiannis et al. (2008) found diminished SICI during the expectation of receiving a reward

although no reward-related response was to be made. Other studies, however, have not found any CS excitability modulation by reward. Radel et al. (2016), for instance, failed to observe differential CS excitability when contrasting intrinsic with extrinsic motivation.

These findings suggest that the perception or anticipation of reward evokes higher CS excitability compared to the perception or anticipation of non-reward. In contrast, the findings described in the present dissertation generally suggest that reward compared to non-reward anticipation is associated with decreased CS excitability during a preparatory period. Although contradictory at first, these findings (i.e., increased vs. decreased CS excitability) may be ascribed to the moment when CS excitability is examined as well as to the underlying cognitive process that is examined. While reward prior to target onset may help to strengthen action preparation, reward after target onset may help to facilitate action execution. Correspondingly, reward does not influence CS excitability per se, but the (observable) effect of reward on CS excitability is dependent on task requirements as well as the moment of stimulation. To avoid too much ambiguity across experimental results, future studies need to employ and maintain task designs and stimulation parameters to permit unequivocal comparison of results across studies.

Related to the discussion above to what extent automaticity is observable in the motor system, the data of Chiu et al. (2014) suggest that reward has an automatic effect on CS excitability. Specifically, these authors reported increased CS excitability 500 ms after an

appetitive cue and decreased CS excitability after an aversive cue, although the to-be given response was unknown at the moment when CS excitability was assessed. Moreover, Gupta and Aron (2011) found that strongly versus weakly urged items evoked increased CS excitability 2500 ms after cue onset although response selection processes were not in place yet. Similarly, several studies in the present dissertation observed increased CS excitability shortly after a cue predicting reward, while no such response was witnessed after a non-reward predicting cue. Such early reward-effect on CS excitability, however, seems to depend on task features such as, for example, to what extent individuals are engaged in the task (c.f., chapter five). Intuitively, however, a fast and valence-dependent response of our brain and specifically of the motor system to appetitive/aversive or reward promising stimuli makes sense, because a quick determination of whether resources in our environment are worth gathering is directly linked to our survival and may eventually enable individuals to quickly engage in consummatory behavior (Schultz, 1998). Although the above mentioned findings may suggest a fast and relatively automatic effect on the motor system and CS excitability, future research is needed to verify this assumption.

Corticospinal excitability and gain modulation by reward

As has been mentioned before, it was proposed that the spotlight's aperture of the gain modulation account may be biased by

task demands (Duque et al., 2017). For example, selecting among multiple action alternatives may result in a narrow spotlight aperture (given the need for selectivity and clear differentiation between action representations). The results from the present dissertation offer another variable that could shape the spotlight's aperture: reward. Accordingly, reward may help to change the spotlight's aperture thereby enhancing its precision. Interestingly, it has been suggested that the reduction of intrinsic neural noise comes at a cost and reward may pay for this cost of control (Manohar et al., 2015). Both lines of research may be in accordance with the findings of the present dissertation, suggesting that reward helps to strengthen control mechanisms, resulting in improved action selection and preparation via a reduction of neural noise. This reduction of neural noise may be associated with reward-related preparatory CS excitability changes in line with the gain modulation account of preparatory CS suppression (Greenhouse et al., 2015b).

Limitations and future directions

The studies discussed in the present dissertation are not without their limitations. One major limitation of our investigation of preparatory CS excitability is the fact that we presented cues that were uninformative regarding the correct upcoming response. However, it is only hardly possible to distinguish preparatory CS excitability based on proclaimed functional accounts if one cannot distinguish between selected and nonselected actions. Consequently,

future research needs to examine the effect of reward (anticipation) on CS excitability and its functional role by allowing to distinguish between selected and nonselected actions. This may easily be implemented by, for example, the presentation of an informative and a reward cue at the beginning of a trial.

Related to the previously described limitation is the fact that the studies described in the current dissertation did not distinguish between different effectors and if or how they were affected by reward-related modulations. However, investigating preparatory CS excitability for task-irrelevant effectors may help to elucidate the functional role of preparatory CS excitability.

Furthermore, some results of present dissertation seem to suggest that reward compared to no-reward prospect is associated with changes time-dependent changes of CS excitability. For instance, chapter three indicated that the prospect of reward was associated with initially increased CS excitability shortly after the motivational cue, and decreased CS excitability just before target onset relative to non-reward prospect (a similar pattern was observed in chapter five, Exp. 2). Although it was speculated that the early component may reflect, for example, reward salience, whether this is actually true remains to be verified. Similarly, how and if early and late reward-related CS excitability is associated remains to be investigated.

To conclude, the present dissertation examined automatic effects on the motor system in extension to previous research. Moreover, it was examined how decision-related variables that are assumed to continuously bias our actions modulate the motor system during action preparation. Both represent promising directions for future research. The investigation of reward-related effects on the motor system, however, may be especially valuable as this field of research is still in its fledgling stages.

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CHAPTER 8

NEDERLANDSTALIGE SAMENVATTING

Het vermogen om door beweging met de omgeving te communiceren en te interageren is waarschijnlijk de meest centrale en belangrijke rol van het menselijk zenuwstelsel. De functies en mechanismen van de hersenen zouden immers grotendeels een epifenomeen blijven als deze niet geïmplementeerd en gerealiseerd konden worden. Beweging wordt gerealiseerd door het motorische systeem, wat bestaat uit hersengebieden zoals de primaire motorische cortex (M1) en hun projecties via het piramidale baan naar het ruggenmerg toe, van waaruit de spieren aangestuurd worden, samen vormen deze delen het corticospinale baan. Maar ook andere hersengebieden zoals de premotorische cortex, de basale ganglia, en de supplementaire motorische cortex spelen een belangrijke rol bij beweging.

Transcraniële magnetische stimulatie (TMS; Hallett, 2007; Rothwell, 1997) kan worden toegepast om de status van het motorische systeem te onderzoeken. Bij deze techniek wordt een magnetische puls boven de primaire motorische cortex (M1) toegediend om onderliggende neuronen te stimuleren, wat excitatie van het corticospinale baan tot gevolg heeft. Deze excitatie van het motorische systeem kan gemeten worden met behulp van elektrodes

die op de spier van de vinger geplaatst worden, waarmee uiteindelijk een manuele respons gemeten wordt (i.e., electromyografie (EMG)). Corticospinale excitatie kan dus geinterpreteerd worden als een maat die aangeeft in hoeverre het motorische systeem actief was op het moment van stimulatie.

Traditioneel werd het motorische systeem en in het bijzonder M1 geassocieerd met het controleren en uitvoeren van beweging (Graziano, 2006; Omrani, Kaufman, Hatsopolous, & Cheney, in press). Dit perspectief is echter aan het veranderen omdat recente bevindingen bijvoorbeeld aantonen dat het motorische systeem ook actief is als een persoon beweging ziet of bewegings-gerelateerde woorden hoort.

Bovendien wordt de activatie van het motorische systeem ook beïnvloed door beslissings-gerelateerde factoren die belangrijk zouden kunnen zijn voor het geven van prioriteit aan een bepaald antwoordalternatief (Bestmann & Duque, 2016; Rizzolatti & Luppino, 2001).

Het motorische systeem wordt dus actief als er een daadwerkelijke beweging uitgevoerd wordt, maar is ook betrokken bij processen die niet of alleen indirect met de uitvoering van een beweging te maken hebben. In het onderzoek beschreven in dit proefschrift werd ten eerste nagegaan in hoeverre abstracte informatie het motorische systeem beinvloedt, om vervolgens ten

tweede te onderzoeken in hoeverre beloning de activiteit van het motorische systeem moduleert.

Eerdere studies hebben aangetoond dat het motorische systeem actief wordt als er bewegings-gerelateerde woorden gelezen of gehoord worden (Hauk, Davis, Ford, Pulvermüller, & Marslen-Wilson, 2006; Hauk, Johnsrude, & Pulvermüller, 2004). Deze studies hebben ook laten zien dat de activatie van het motorische systeem afhangt van de betekenis van het gehoorde of gelezen woord – het woord "grijpen" is bijvoorbeeld geassocieerd met de activatie van hand-gerelateerde hersengebieden maar niet met de activatie van voet-gerelateerde hersengebieden. In hoofdstuk 2 hebben wij TMS gebruikt om te onderzoeken in hoeverre het motorische systeem ook gevoelig zal zijn voor abstracte, spatiële stimuli (i.e., het woord LINKS, RECHTS, of XXXXX) die geen daadwerkelijke beweging vereisen. De resultaten lieten een congruentie effect zien in de zin dat het woord LINKS (RECHTS) tot verhoogde activiteit in de rechter (linker) M1 leidde. Deze resultaten geven aan dat hoewel er geen (manuele) respons gegeven moest worden, het motorische systeem ook actief wordt als de hersenen abstracte informatie ageboden krijgt.

In hoofdstuk 3 hebben wij onderzocht in hoeverre de activiteit van het motorische systeem gemoduleerd kan worden door beloning. Deelnemers moesten een cue-target-delay paradigma doorlopen (Simon taak) waarbij een beloningscue aan het begin van de trial aangaf of er wel of geen beloning voor een correcte en snelle manuele

respons verdiend kon worden. Na de presentatie van deze cue volgde een korte wachtperiode en werd TMS over de linker M1 toegepast. Hierdoor konden we het effect van (geen) beloning op het motor systeem tijdens het voorbereiden van een motorische response bestuderen. Na deze wachtperiode volgde de presentatie van de target (een gekleurde cirkel links of rechts van het fixatiepunt) waarop deelnemers moesten reageren met de linker of rechter wijsvinger. De resultaten lieten zien dat het motorische systeem minder activatie toonde tijdens de preparatie van een motorische respons als deze responsgeassocieerd was met beloning, dan wanneer de motorische respons niet geassocieerd was met een beloning).

Hoofdstuk 4 was bedoeld om de bevindingen uit hoofdstuk 3 te repliceren en uit te breiden.In plaats van een Simon taak voerden de deelnemers een Stroop taak uit. Resultaten lieten zien dat het motorische systeem niet door beloning gemoduleerd werd, wat suggereert dat het effect van beloning op de activatie van het motorische systeem afhankelijk is van de taak die deelnemers moeten voorbereiden en uiteindelijk uitvoeren.

In Hoofdstuk 5 onderzochten we het effect van beloning op het motorische systeem als er wel of geen motorische respons voorbereid moest worden. Aan het begin van elke trial werd aangegeven of er wel of niet een motorische respons uitgevoerd moest worden. Hierna volgde het cue-target-delay paradigma dat boven gespecificeerd werd. Resultaten lieten zien dat beloning geen effect heeft op de

activatie van het motorische systeem als personen weten dat er geen motorische respons voorbereid hoeft te worden. Verder lieten de resultaten zien dat het effect van beloning op het motorische systeem ook afhangt van tijdsdruk als gevolg van bijvoorbeeld een (strikte) deadline voor het geven van de motorische respons.

Hoewel uit de voorafgaande hoofdstukken bleek dat beloning een effect op het motorische systeem heeft, blijft het onduidelijk waar in het motorische systeem beloning dit effect uitoefent. Deze vraag werd in hoofdstuk 6 nagegaan, door te onderzoeken of beloning een effect heeft op inhibitie binnen de hersenen (Di Lazzaro & Rothwell, 2014; Kujirai et al., 1993). De resultaten toonden aan dat beloning geen effect heeft op inhibitie, wat suggereert dat belonings-gerelateerde veranderingen in het motorisch systeem te wijten zijn aan veranderingen in excitatie van het corticospinale baan.

Samengevat laat het onderzoek dat beschreven werd in dit proefschrift zien dat het motorische systeem niet alleen betrokken is wanneer een daadwerkelijke beweging dient te worden gecontroleerd of uitgevoerd, maar ook zonder dat of voordat een motorische handeling wordt uitgevoerd. Alhoewel wij aangetoond hebben dat het motorische systeem (minder) actief wordt bij het ontvangen van abstracte informatie, is het nog onduidelijk onder welke voorwaarden deze activiteit tot stand komt. Bovendien laat dit proefschrift zien dat (wel of geen) beloning het motorische systeem op verschillende manieren kan beinvloeden tijdens het plannen van een beweging. Dit effect van beloning op het motorische systeem is

afhankelijk van verschillende factoren zoals tijdsdruk en het plannen van een daadwerkelijke beweging. Toekomstig onderzoek kan zich toespitsen op de neurale oorsprong en de functie van deze modulatie van het motorische systeem.

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DATA STORAGE FACT SHEETS

In compliance with the UGent standard for research accountability, transparacy and reproducibility, the location of the datasets used in this dissertation are added below. For each of the empirical chapters (i.e., chapters 2 to 6) a separate Data Storage Fact Sheet is completed, detailing which data and analysis files are stored, where they are stored, who has access to the files and who can be contacted in order to request access to the files. In addition, the Data Storage Fact Sheets have been added to my public UGent Biblio account.

DATA STORAGE FACT SHEET FOR CHAPTER 2

```
% Data Storage Fact Sheet

% Name/identifier study: It wasn't me! Motor
activation from irrelevant spatial information
in the absence of a response
% Author: Carsten Bundt
% Date: 28-08-2017


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==========================================
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1a. Main researcher
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2. Information about the datasets to which this sheet applies
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* Reference of the publication in which the datasets are reported:

Bundt, C., Bardi, L., Abrahamse, E. L., Brass, M., & Notebaert, W. (2015). It wasn't me! Motor activation from irrelevant spatial information in the absence of a response. Frontiers in Human Neuroscience, 9.

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DATA STORAGE FACT SHEET FOR CHAPTER 3

```
% Data Storage Fact Sheet

% Name/identifier study: Reward anticipation
modulates primary motor cortex excitability
during task preparation
% Author: Carsten Bundt
% Date: 28-08-2017


1. Contact details
==========================================
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1a. Main researcher
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2. Information about the datasets to which this sheet applies
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Bundt, C., Abrahamse, E. L., Braem, S., Brass, M., & Notebaert, W. (2016). Reward anticipation modulates primary motor cortex excitability during task preparation. NeuroImage, 142, 483-488.

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DATA STORAGE FACT SHEET FOR CHAPTER 4

```
% Data Storage Fact Sheet

% Name/identifier study: Reward does not alter
corticospinal excitability during Stroop task
preparation
% Author: Carsten Bundt
% Date: 28-08-2017


1. Contact details
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2. Information about the datasets to which this sheet applies
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* Reference of the publication in which the datasets are reported:

Bundt, C., Boehler, C. N., Verbruggen, F., Brass, M., & Notebaert, W. Reward does not alter corticospinal excitability during Stroop task preparation. *Manuscript in preparation.*

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DATA STORAGE FACT SHEET FOR CHAPTER 5

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% Data Storage Fact Sheet

% Name/identifier study: Reward anticipation
changes corticospinal excitability during task
preparation depending on response requirements
and time pressure.
% Author: Carsten Bundt
% Date: 28-08-2017


1. Contact details
==========================================
============

1a. Main researcher
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Bundt, C., Bardi, L., Verbruggen, F., Boehler, C. N., Brass, M., & Notebaert, W. Reward anticipation changes corticospinal excitability during task preparation depending on response requirements and time pressure. *Manuscript in preparation.*

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DATA STORAGE FACT SHEET FOR CHAPTER 6

```
% Data Storage Fact Sheet

% Name/identifier study: No evidence of reward
prospect modulating short intracortical
inhibition during action preparation.
% Author: Carsten Bundt
% Date: 28-08-2017


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